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Applicant	:	David R. Hennings	
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Title	:	Endovenous Closure of Varicose Veins with Mid-Infrared Laser	
Group Art Unit	:	3735	
Examiner	:	David M. Shay	
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Alexandria, VA 22313-1450

SUPPLEMENTAL APPEAL BRIEF AND REQUEST FOR ORAL HEARING

Sir:

Real Party in Interest

CoolTouch, Inc., a wholly-owned subsidiary of New Star Laser Company, is the real party in interest.

Related Appeals and Interferences

None.

CERTIFICATE OF MAILING, 37 CFR §1.8

I hereby certify, pursuant to 37 CFR §1.8, that I have reasonable basis to expect that that this paper or fee (along with any referred to as being attached or enclosed) would be mailed or transmitted on or before the date indicated with the United States Postal Service with sufficient postage as first class mail on the date shown below in an envelope addressed to the Commissioner for Patents, Mail Stop Appeal Brief-Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Dated: September 11, 2009

Lynne Fulmer

Status of Claims

Claims 1-17 and 19-23 and 25-46 are pending in this application. These claims have all been rejected and are the claims on appeal. Claims 18 and 24 have been cancelled.

Status of Amendments

All amendments which Applicant has filed have been entered.

Summary of Claimed Subject Matter

There are four independent claims, which are claims 1, 14, 25 and 35, in the present application. Claims 1, 25 and 35 are method claims and claim 14 is a system claim, all of which are directed to the treatment varicose veins.

Claim 1 reads as follows:

> "1. An endovenous method of treating a varicose vein comprising the step of using a laser having a wavelength between about 1.2 and about 1.8 um to heat and shrink collagen in a varicosed vein to destroy the functionality of the varicose vein."

This method is illustrated schematically in Figures 3A-6 and in more detail in Figures 7 and 8. As described in paragraphs 47-50 of the application, the method comprises using a laser fiber 306 (which has been deployed through dilator 300) into vein 202. This is described in paragraph 47 of the specification as follows:

> "FIG. 3B is a representative view showing the use of the introducer or dilator 300 with the laser fiber 306 passing through the lumen 302 of the dilator 300 and into the GSV (greater saphenous vein) 202 ..."

The use of a laser having a wavelength between about 1.2 and about 1.8 um is described in paragraph 52 as follows:

> "The 1.2 to 1.8 um laser wavelengths are ideally suited to penetrate the small amount of remaining blood in the vessel 200 but also is much more strongly absorbed in the vessel wall 704 by collagen. Most of the energy is concentrated in the wall 704 for heating and shrinkage and is not transmitted through to surrounding tissue 702."

Claims 2-13, 26, 29, 32, 37 and 41 are dependent, directly or indirectly on claim 1. Claims 2, 3, 6, 26, 29, 32, 37 and 41 are directly dependent upon claim 1. Claims 4 and 5 are dependent upon claim 3. Claims 7-9 and 12 are dependent upon claim 2. Claims 10-13 are dependent upon claim 9. Claim 2 recites the use of a fiber optic which is disclosed at page 13, line 19 and illustrated in Figure 1 as element 106. Claims 3-5 are directed to the use of a pullback device which is disclosed at page 13, line 19 and original claim 3 and illustrated in Figure 1 as element 104. Claim 6 recites the preliminary step of removing blood from a vein prior to treatment with laser energy, page 15, lines 17 and 18. Claim 7 recites the use of an introducer catheter to introduce the fiber optic into the vein which is disclosed at page 14, lines 3-5 and illustrated in Figure 3B in which the introducer is shown as element 300. Claim 8 is directed to the use of a diffusing tip fiber optic which is disclosed at page 18, line 4 through page 20, line 2 and illustrated in Figures 9A, 9B and 9C. Claims 10-13 are directed to the use of a thermal sensor which is described at page 16, line 13 through page 18, line 2 and illustrated in Figure 6 in which the thermal sensor is shown as element 600. Claim 26 recites that the laser energy has a wavelength of about 1.32 um which is disclosed at page 12, line 23, page 16, line 2, 20, line 16, page 20, line 24, page 22, line 5 and page 23, line 22, for example. The use of a Nd:YAG laser is disclosed, for example, at page 16, line 1, page 24, line 2 and at page 22, line 25. Claim 32 recites that the laser energy preferentially heats the water in the wall of the vein which is disclosed at page 9 line, 10 and at page 23, lines 22 and 23, for example. Claim 41 is directed to

heating the target chromophore to a temperature not greater than 85° C which is disclosed at page 8, line 14.

Claim 14 reads as follows:

> "14. A system for endovenous treatment of varicose veins comprising the following:
> A laser having a wavelength between about 1.2 and about 1.8 um; and
> A fiber optic laser delivery device having a proximal end and a distal end, for delivery of laser energy from the distal end of the fiber optic laser delivery device to the inside wall of a varicose vein wherein the functionality of the varicose vein is destroyed and collagen in the varicosed vessel wall can be heated and shrunk."

The system of claim 14 is illustrated in Figure 1 and in more detail in Figure 3B. In Figure 1, laser console 102 is illustrated and it is disclosed in paragraph 54 that laser 102 can be used to provide laser wavelengths in the 1.2 to 1.8 um region. In Figure 3B, the fiber optic laser device 306 is illustrated and described in paragraph 47 as follows:

> "FIG. 3B is a representative view showing the use of the introducer or dilator 300 with the laser fiber 306 passing through the lumen 302 of the dilator 300 and into the GSV (greater saphenous vein) 202 ..."

The function of this system to deliver energy to heat and shrink the collagen in the vessel wall is described as follows in paragraph 52:

> "The 1.2 to 1.8 um laser wavelengths are ideally suited to penetrate the small amount of remaining blood in the vessel 200 but also is much more strongly absorbed in the vessel wall 704 by collagen. Most of the energy is concentrated in the wall 704 for heating and shrinkage and is not transmitted through to surrounding tissue 702."

Claims 15-17, 19-23, 27, 30 and 33 are dependent, directly or indirectly, upon claim 14. Claims 15-17, 21, 27, 30 and 33 are directly dependent on claim 14. Claims 19 and 20 are

dependent on claim 17. Claim 22 is dependent on claim 21 and claim 23 is dependent on claim 23. Claim 15 recites a pullback device which is disclosed at page 13, line 19 and illustrated as element 104 in Figure 1. Claim 16 recites the administration of anesthesia to cause swelling and compression of the tissue surrounding the varicose vein which is disclosed at page 14, lines 15-18 and illustrated in Figure 7. Claim 17 recites an introducer catheter which is disclosed at page 14, lines 3-5 and illustrated in Figure 3B as element 300. Claims 19 and 20 recite a diffusing tip on the fiber optic which is disclosed at page 18, line 4 through page 20, line 2 and illustrated in Figures 9A, 9B and 9C. Claims 21-23 recite a thermal sensor and temperature controller which are disclosed at page 16, line 13 through page 18, line 2 and illustrated in Figure 6. Claim 27 recites a laser having a wavelength of 1.32 um which is disclosed, for example, at page 12, line 23, page 16, line 2, page 20, line 24, page 22, line 25, page 23, line 22 and page 24, line 2. Claim 30 recites a Nd:YAG laser which is disclosed at page 16, line 1, page 22, line 25 and page 24, line 2. Claim 33 recites that the system is adapted to preferentially heat water which is disclosed, for example, at page 23, lines 22 and 23 and illustrated in Figure 10.

Claim 25 reads as follows:

> "25. An endovenous method of treating varicose veins with laser energy to heat and shrink collagen in the vein and to destroy the functionality of the varicosed vein, the method comprising the following steps:
> inserting a laser delivery device into the varicose vein;
> delivery laser energy having a wavelength between about 1.2 and about 1.8 um to the varicose vein; and
> retracting the laser delivery device through the varicose vein, thereby heating and shrinking the collagen in the vein and destroying the functionality of the varicose vein."

The first two steps of claim 25 are illustrated and described as set forth above with regard to claim 1. The step of retracting the laser delivery device is described in paragraph 51 as follows:

> "The catheter 32 is connected to a motorized pullback device 104 either inside or outside of the sterile field 108 of the patient. The procedure begins by starting the pullback for about 2 or 3 mm and then turning the laser 102 on at about 5 watts of power. The pullback device is illustrated schematically in Figure 1 as element 104. "

Claims 28, 31 and 34 are each directly dependent on claim 25. Claim 28 recites that the laser has a wavelength of about 1.32 um as disclosed, for example, at page 23, line 22, page 12, line 33, page 16, line 2, page 22, line 5 and page 20, line 16. Claim 31 recites a Nd:YAG laser as disclosed at page 16, line 1. Claim 34 recites that the laser energy preferentially heats water as described at page 9, line 10 and at page 23, lines 22 and 23 and illustrated in Figure 10.

Claim 35 reads as follows:

> "35. A method of treating varicose veins, comprising
> providing a beam of light comprising a wavelength in the range of about 1200 nm to about 1800 nm; and
> delivering endovascularly the beam of light to target a chromophore comprising water in the wall of a targeted varicose vein to treat the vein."

This method is illustrated in Figure 3B and is described in paragraph 47 as follows:

> "FIG. 3B is a representative view showing the use of the introducer or dilator 300 with the laser fiber 306 passing through the lumen 302 of the dilator 300 and into the GSV (greater saphenous vein) 202..."

According to the preferred embodiment of the method and apparatus of the present invention. the method is further described in paragraph 52 which states:

> "The 1.2 to 1.8 um laser wavelengths are ideally suited to penetrate the small amount of remaining blood in the vessel 200 but also is

> much more strongly absorbed in the vessel wall 704 by collagen. Most of the energy is concentrated in the wall 704 for heating and shrinkage and is not transmitted through to surrounding tissue 702."

Water absorption of laser energy in the region between about 1200 nm to about 1800 nm is disclosed in paragraph 65 and is illustrated in Figure 10. In paragraph 65, it is stated:

> "It will further be observed that the region between about 1200 nm to about 1800 nm shows low hemoglobin and higher water absorption, which is a key to the present invention."

Claims 38-40 and 42-46 are dependent, directly or indirectly, on claim 35. Claims 38, 40, 44 and 45 depend directly on claim 35. Claims 39 and 42 depend on claim 38, claim 43 depends on claim 42 and claim 46 depends on 45. Claim 38 is directed to the use of a fiber optic which is disclosed at page 13, lines 19 and 20 and illustrated in Figure 1 wherein element 106 is the fiber optic. Claim 39 recites the use of a diffusing tip which is disclosed at page 18, line 3 through page 20, line 2 and illustrated in Figures 9A, 9B and 9C. Claim 40 recites that the treatment reduces the size of the varicose vein which is disclosed at page 20, lines 20-22. Claims 42 and 43 recite the use of a pullback device which is disclosed at page 13, lines 19 and 20, original claim 2 and illustrated in Figure 1 where the pullback machine is element 104. Claim 44 recites removing blood from the vein prior to treatment which is disclosed at page 14, line 20. Claim 45 recites the laser power of 1 to 20 watts which is disclosed at page 15, lines 12 and 13. Claim 46 recites a power of 5 watts which is disclosed at page 15, line 12.

With further regard to the dependent claims, the fiber optic delivery device of claims 2, 14 and 38 is illustrated as element 306 in Figure 3B and is described in paragraph 47.

The procedure of claim 5 in which the pullback device begins retraction of the fiber optic device prior to initiating delivery of the laser energy is disclosed in paragraph 51.

The use of a diffusing tip on the optical fiber recited in claims 8, 19 and 39 is illustrated in Figures 9A, 9B and 9C and is described in paragraphs 62, 63 and 64 as well as in paragraphs 59-61.

The non-contact thermal sensor of claims 9 and 21 is described in paragraphs 55 and 56. Providing the fiber optic laser delivery device with a thermal sensing element as recited in claim 12 is described in paragraph 55.

The procedure of modulating the laser power based on the sensed temperature as recited in claims 13 and 23 is described in paragraph 55.

The use of a laser having a wavelength of about 1.32 um as recited in claims 26-28 and 37 is disclosed in paragraph 53 and paragraph 79.

The use of a Nd:YAG laser as recited in claims 29-31 is disclosed in paragraphs 53 and 54.

The preferential heating of water in the wall of the vein as recited in claims 33-35 is disclosed in paragraphs 65 and 79. It is also disclosed in paragraph 21.

The use of laser power between about 1 to about 20 watts as recited in claim 45 and the use of laser power of about 5 watts as recited in claim 46 is described in paragraph 51.

There are four independent claims, which are claims 1, 14, 25 and 35. Claims 1, 25 and 35 are directed to a method of treating varicose veins and claim 14 is directed to a system for treating varicose veins. Method claims 1 and 25 and system claim 14 recite treatment using a laser having a wavelength between about 1.2 um (1200 nm) and about 1.8 um (1800 nm). Claim 35 recites a method using this range of wavelengths to target a chromophore comprising water in the wall of a targeted varicose vein.

The method of claims 1, 25 and 35 is illustrated schematically in Figures 3A-6. The method is illustrated in more detail in Figures 7 and 8. This method is described in paragraphs 47-50 of the application. The method comprises introducing a dilator 300 into the vein to be treated with the laser fiber 306 passing through a lumen 302 of the dilator 300 and into vein 202. Once the laser fiber is properly positioned, laser energy is passed therethrough at a wavelength of about 1.2 to about 1.8 um to preferentially heat the water in the wall of the vein rather than blood which maybe present in the vein.

The use of a pull back device 104 is disclosed in paragraph 51 of the application. The use of the diffusers 902, 920 and 926 illustrated in Figures 9A-C is disclosed in paragraph 62-64 of the application. The use of thermal detector 600 is illustrated in Figure 6 and is described in paragraphs 55-57 of the application.

The system of claim 14 comprising a laser 102 and a fiber optic delivery device 306 is illustrated in Figures 1 and 3A-8.

The preferential absorption of laser energy by the water in the wall of a targeted varicose vein recited in claim 35 is disclosed in paragraphs 21, 52, 65, 79, and FIG. 10 of the application. This localizes the heating caused by the laser energy in the vessel wall 704 thereby significantly inhibiting the heating of surrounding tissue 702 as described in paragraphs 22, 23, 52, and 79.

Grounds of Rejection To Be Reviewed on Appeal

Claims 1, 2, 6, 7, 25, 35-38, 40, 41 and 44-46 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Goldman Patent No. 6,258,084 in combination with Sinofsky Patent No. 5,196,004 and Dew Patent No. 4,854,320. Claims 3-5, 42 and 43 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Goldman in combination with Sinofsky, Dew and Roth

Patent No. 5,207,672. Claims 8 and 39 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Goldman in combination with Sinofsky, Dew and Conn PCT Application No. WO 92/17243. Claims 9-13 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Goldman, in combination with Sinofsky, Dew and Makower PCT Application No. WO 93/15664. Claims 14-17 and 20-23 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Makower, in combination with Roth and Dew. Claim 19 has been rejected as unpatentable over Makower, in combination with Dew, Roth and Conn.

Claims 1, 2, 6, 7, 25, 35-38, 40, 41 and 44-46 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Goldman Patent No. 6,258,084 in combination with Sinofsky Patent No. 5,196,004 and Dew Patent No. 4,854,320. Claims 3-5, 42 and 43 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Goldman in combination with Sinofsky, Dew and Roth Patent No. 5,207,672. Claims 8 and 39 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Goldman in combination with Sinofsky, Dew and Conn PCT Application No. WO 92/17243. Claims 9-13 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Goldman, in combination with Sinofsky, Dew and Makower PCT Application No. WO 93/15664. Claims 14-17 and 20-23 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Makower, in combination with Roth and Dew. Claim 19 has been rejected as unpatentable over Makower, in combination with Dew, Roth and Conn.

Evidence Appendix

Applicant has submitted declarations under 37 CFR 1.132 together with exhibits. These declarations and exhibits are attached hereto as an evidence appendix in conformance with 37 CFR

41.37(c)(1)(ix) as Appendix 2. This evidence was entered by the Examiner in the Office Action dated March 13, 2009.

Historical Note

This Appeal has something of an unusual history. This is not the first Appeal Brief to be filed in this application and the Office Action dated March 13, 2009, is not the first Final Rejection from which an Appeal has been taken. The earlier appeal never got past the Examiner's Answer stage because a new ground of rejection was raised in that Answer.

There was an earlier Final Rejection dated February 12, 2007 from which Applicant appealed and filed an Appeal Brief on October 29, 2007 (which was objected to on formal grounds and Applicant filed a corrected appeal brief on November 28, 2007). Almost one year later, the Examiner filed an Examiner's Answer on November 13, 2008 stating that it was in response to an appeal brief filed "November 28, 2008" (sic), (November 28, 2007 was the actual date). This Board noted that the Examiner's Answer made a new ground of rejection and Applicant was given the option of requesting that prosecution be re-opened under 37 CFR 1.111. Applicant did request re-opening of prosecution and, on January 13, 2009, responded to the new ground of rejection set forth in the Examiner's Answer. This response included a Declaration of David R. Hennings dated December 22, 2008 (which was the second Hennings Declaration to be filed in this application) and the Declaration of Mitchel P. Goldman dated December 23, 2008, together with Exhibit 1 to the Hennings Declaration and Exhibits 1-3 to the Goldman Declaration. The Examiner then rendered another Final Rejection dated March 13, 2009 and it is this Final Rejection to which the present Appeal is directed.

The issues presented in this Appeal involve both (a) the usual comparison of the claims with the prior art and (b) the Examiner's refusal to give effect to the evidence submitted in support of patentability. Thus, we will first discuss the prior art rejections and why we believe they are erroneous and then discuss the extensive evidence which conclusively refutes the Examiner's positions and what we believe to be the Examiner's improper refusal to give this evidence the weight to which it is entitled.

The Rejections Are In Error

Claims 1, 2, 6, 7, 25, 35-38, 40, 41 and 44-46 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Goldman '084 in combination with Sinofsky Patent No, 5,196,004 and Dew et al. Patent No. 4,854,320. Goldman is directed almost entirely to RF heating of varicose veins and contains only one throw-away sentence which mentions lasers at column 7, lines 53-59, and which says that "other forms of energy such as microwaves, ultrasound, direct current, unrelated heated fluid, radiant light, and lasers can be used....". This single mention of lasers in Goldman is non-enabling and occurs only in the context of a listing of several possible alternatives to the use o RF energy, none of which are otherwise mentioned or enabled.

The law relating to enablement, and the lack of it, makes it plain that making a passing reference to an alternate system does not constitute compliance with the enablement requirement of 35 USC 112. For example, in Sitrick v. Dreamworks, LLC, 516 F.3d 993 (Fed. Cir. 2008), the patent was directed to an intercept adapter interface system (IAIS) and a Controller 260C for integrating images into a predefined audio/visual presentation. The '825 patent-in-suit disclosed that "this invention relates to predefined video and audio/visual presentations such as **movies** and **video games**", but the remaining disclosure was directed in its entirety to video games and there was **no**

further disclosure relating to movies. At 516 F.3d 1000, the Court noted, "the specifications do not disclose how the IAIS or Controller 260C would function for movies" and went on to say that the "patents do not teach how to implement the internal 'intercept logic functioning' of Controller 260C in the context of movies." The Federal Circuit then held, 516 F.3d 1002-03 that "all asserted claims of the '825 patent are not enabled."

Similarly, in Auto. Techs. International v. BMW of N.Am., Inc., 501 F.3d 1274, 1285 (Fed. Cir. 2007), the Federal Circuit said:

> "Disclosure of only mechanical side impact sensors does not permit one skilled in the art to make and use the invention as broadly as it was claimed, which includes electronic side impact sensors."

The Federal Circuit's decision in Medtronic Navigation, Inc. v. Brainlab, 222 Fed. Appx. 952 (Fed. Cir. 2007), which was not selected for publication in the Federal Reporter and is not precedential, nevertheless serves as a useful guide to the state of the law on enablement. In Medtronic, the patent was directed to an acoustic or ultrasound range finding system and to an electromagnetic position and orientation system to track the movement of an object, but also contained the statement:

> "An optical system can be used as an alternative to the acoustic system described earlier."

There was no other disclosure relating to an optical system. The Federal Circuit held:

> "There is no enabling description of how to make and use an optical tracking system...."

Thus, although Medtronic is not precedential, it is consistent with Sitrick with regarding to finding a lack of enablement when a specification contains nothing more than a single disclosure of

an otherwise unmentioned alternative. So it is here. There is but a single word in Goldman relating to lasers without any further mention of such devices.

As stated in Fiers v. Revel, 984 F.2d 1164, 1171 (Fed. Cir. 1993) such a minimal, non-enabling disclosure is "an attempt to preempt the future before it has arrived."

Furthermore, we have the benefit of the acknowledgement of Goldman himself that the '084 patent does not enable lasers or laser treatment of varicose veins. Goldman's own Declaration dated December 23, 2008, in paragraph 5, states:

> "The work upon which my Patent No. 6,258,084 is based involved only the use of tumescent anesthesia in the RF treatment of varicose veins and no work of any sort was done involving the use of lasers. Prior to filing the application which became Patent No. 6,258,084, we had no experience or knowledge which would permit us to enable the use of lasers to treat varicose veins. For example, we did not know which laser wavelengths might be useful nor did we know what power levels might be safe and effective."

This is a direct and unequivocal statement by one of the inventors of the Goldman '084 patent (who is also one of the inventors named in the present application) that his '084 patent is not enabling with regard to lasers. As we will discuss in more detail below, the Examiner, at pages 6 and 7 of the Final Rejection, attempts to sidestep the Goldman Declaration by resorting to:

1. The totally irrelevant fact that claim 31 of the Goldman '084 patent does not recite tumescent anesthesia;

2. A refusal to recognize that the word "we" in the Goldman Declaration refers to Goldman and his co-workers; and

3. A seriously misguided attempt to find an inconsistency between the Goldman Declaration and the oath of inventorship in the '084 patent.

The Examiner's arguments are misplaced and unsupported. In brief:

1. The absence of a recitation of tumescent anesthesia in claim 31 of the '084 patent has absolutely nothing to do with whether lasers are enabled;

2. The word "we" in Goldman's Declaration plainly refers to Goldman and his co-workers on the subject matter of the '084 patent; and

3. The Examiner has built a house-of-cards argument based on the inventors oath in the '084 patent because **none of the original claims recited a laser!**[1] Thus, there is absolutely no inconsistency between the inventors' oath in the '084 patent and the Goldman Declaration. Furthermore, even if the original claims did recite a laser, no court has ever mentioned an inventor's oath as having any consequence when making a determination regarding enablement.

Thus, the Examiner's conclusion as stated at page 7 of the Final Rejection as follows:

> "Thus, weighing Declarant's statement, wherein Declarant holds a vested interest in the issuance of the instant application, against the evidence afforded by a signed declaration in a U.S. patent (which includes a presumption of operability), the examiner is not persuaded by Declarant's current stance, that the subject matter of the claims of the Goldman et al. ('084) is inoperable."

is devoid of any support in the record. Furthermore, the issue is **not** the **operability** of the **claims** of the Goldman '084 patent, but rather the lack of **enablement** of lasers in the **specification** of that patent.

[1] Applicants ask that this Board take judicial notice of the original claims of the application which became the '084 patent. For the convenience of the Board, these claims are provided in the appendix to this brief.

The '084 patent discloses nothing with regard to laser wavelengths or power levels. The choice of laser wavelengths is of crucial importance. Unlike conductive and connective heating, laser heating is highly selective and the laser will only heat materials which are a chromophore for a given wavelength, but not other materials which are not chromophores for that wavelength. The claims in the present application recite a wavelength of about 1200-1800 nm which was a departure from the prior laser treatment of varicose veins (which the Examiner has refused to regard as meaningful) such as Navarro Patent No. 6,398,777 which discloses the use of lasers having wavelengths of 500-1100 nm.

Thus, merely mentioning lasers generally, as Goldman '084 does, leaves the reader entirely in the dark as to what lasers, with what wavelengths, for what chromophores might be tried in an effort to treat varicose veins. This is the very definition of undue experimentation. In addition, the type of laser, power levels and duration of treatment must also be determined requiring even more experimentation. Some of the factors to consider in the experimentation required to determine the type of laser, the laser wavelength, the power levels and dose duration for a given use are outlined in Sinofsky Patent No. 5,196,004, in cols. 2-5.

This lack of disclosure in Goldman is also in contrast to the disclosure in Navarro Patent No. 6,398,777,[2] which is regarded by those in the art as representing the first use of lasers to treat varicose veins, which, at col. 5, lines 17-23, at col. 6, lines 13-18 and at col. 5, lines 45-49, discloses wavelengths of 50-1100 nm, power levels of 5 to 20 watts and treatment duration of 0.2-10 seconds.

[2] The Examiner has steadfastly and mysteriously refused to rely on the Navarro patent as a reference, *see* p. 3, lines 2-13, of the Final Rejection.

Thus, Navarro provides the type of disclosure which is entirely lacking in Goldman's '084 single nonenabling mention of lasers.

Since Goldman '084 is nonenabling, the attempt to combine Sinofsky and Dew et al. with Goldman is an exercise in futility and the rejection of claims 1, 2, 6, 7, 25-38, 40, 41 and 44-46 over this combination of references cannot stand.

Furthermore, even if Goldman '084 were enabling, this rejection would be in error because the secondary references do not remedy the deficiencies of Goldman and are completely unrelated to Goldman and to each other and cannot be properly combined. Goldman '084 relates to treatment of varicose veins, Sinofsky is directed to removal of atherosclerotic plaque and Dew et al. is concerned with wound healing. Goldman says nothing at all about laser wavelengths and thus gives no guidance with regard to the 1200-1800 nm range recited in the appealed claims. Nor does Goldman say anything with regard to choice of chromophores and has no appreciation of the different chromophore characteristics of the tissues and fluids associated with varicose veins or of the importance of those chromophore characteristics in choosing a laser having a desirable wavelength.

Sinofsky, who discloses a preferred laser treatment of arterial plaque with laser energy in the range 1900-2100 nm (column 3, lines 15-19), also discusses the characteristics of various types of lasers and discloses tissue removal with laser energy in the range 1400-2200 nm (column 2, line 63). In fact, Sinofsky's discussion of lasers of different types with wavelengths ranging from 200-2200 nm at columns 2-4 makes it clear that the selection of a wavelength suitable for a given target must include not only the absorption characteristics of the target, but also the absorption characteristics of materials which are not the target but which are in the path of the laser energy, to avoid unacceptable energy loss before the energy reaches the target. These characteristics must be taken into account,

but the Goldman '084 patent failed to even recognize this need, much less enable the choice of laser, choice of wavelength, etc.

Dew et al. disclose the use of an Nd:YAG laser tuned from its normal wavelength of 1064 nm to its "secondary wavelength" of 1320 nm, col. 4, lines, 11-14, but not for varicose vein treatment and not for treatment of plaque, but rather for wound healing and tissue repair by solubilizing collagen. In addition, Dew's 1320 nm is outside Sinofsky's lower limit of 1400 nm, and Dew's range of 1200-1400 nm is adjacent to the 1400-2200 nm range of Sinofsky. There is no disclosure in Sinofsky of a Nd:YAG laser of any type and no disclosure of tuning such a laser to its secondary wavelength of 1320 nm. Thus, the wavelength choices in Sinofsky and Dew et al. are antithetical to each other, as are their respective targets, and these references cannot be properly or sensibly combined.

Based on this gallimaufry of references, the Examiner states at p. 15 of the Final Rejection:

> "It would have been obvious to the artisan of ordinary skill to employ the wavelength of Dew et al. in the method of Goldman et al ('084) wince Goldman ('084) teach no particular wavelength, and since the wavelength of Dew et al. can destroy (denature) the proteins, but allow near normal tissue to take it's (sic) place. (See Dew et al., column 11, lines 37-44) and since this wavelength is highly absorbed as taught by Sinofsky, thus producing a method such as claimed."

To state this proposition is to refute it. The notion that the failure of Goldman to provide any guidance with regard to wavelength leaves the Examiner free to pick any reference that discloses, for any purpose, a wavelength that comes within applicants' claimed range and combine it with Goldman demonstrates a very serious lack of reasoning and has no rational underpinning. Rather, the Examiner was motivated only by applicants' claims to attempt a reconstruction of applicant's

invention. To then toss Sinofsky into the pot for his teaching that plaque will absorb laser energy at 1400-2200 nm (column 5, lines 17-21) adds a reference which has nothing to do with Goldman (or Dew et al.) and operates in a range which is essentially different from and antithetical to that of Dew et al., a difference which stems from the fact that the purpose and the target of Sinofsky are entirely different from those of Dew et al.

Plainly, the Examiner has not made a prima facie case of obviousness by relying on such disparate references. In the time subsequent to the decision in KSR International v. Teleflex, Inc., 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), this Board has repeatedly recognized that rejections should be reversed when the Examiner fails to articulate reasoning with a rational underpinning for combining the prior art. For example, in Ex Parte Erkey et al., Appeal No. 20071375, decided May 11, 2007, this Board said:

> "We determine that the examiner has not provided a sufficient reason or explicit analysis of why the disclosures of the references should be combined."

Similarly, in Ex Parte Crawford et al., Appeal 20062429, decided May 30, 2007, this Board reversed a rejection and said:

> "We find no suggestion to combine the teachings and suggestions of [the references] as advanced by the examiner, except from using appellant's invention as a template through a hindsight reconstruction of appellant's claims."

We submit that the Examiner in the present case has done precisely the same thing as the Examiner in Crawford. Furthermore, it is important to note that KSR cited the decision in In Re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006) with approval. In Kahn, the Federal Circuit stated:

"[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."

In the present case, the Examiner has provided neither articulate reasoning nor a rational underpinning to support his rejection. Rather, he has used the silence in Goldman with regard to laser wavelength as a blank check in his effort to reconstruct the claimed invention by relying on the unrelated disclosures of Sinofsky and Dew et al.

Claims 3-5, 42 and 43 have been rejected as unpatentable under 35 U.S.C. § 103(a) over Goldman '084 in combination with Sinofsky, Dew and Roth. These claims recite a pull back device and Roth, in an entirely different context, also discloses a pull-back device. The most important point is that the Roth reference, which is directed to the treatment of benign prostate hypoplasia (BPH), does nothing to cure the deficiencies in the attempted combination of Goldman, Sinofsky and Dew et al. Furthermore, the Examiner provides no reasoning or rational underpinning for combining Roth with Goldman, Sinofsky and Dew et al. They are all directed to different fields of use. Thus, the rejection of these claims is in error.

Claims 8 and 39 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Goldman '084 in combination with Sinofsky, Dew, and Conn. Conn teaches a diffusing tip. Applicant does not purport to be an inventor of a diffusing tip for a laser and points out that Conn does nothing to cure the deficiency of the attempted combination of Goldman with Sinofsky and Dew. Furthermore, the Examiner has not provided reasoning or a rational underpinning for combining Conn with the remaining references. It is only an attempt to reconstruct applicants' invention which inspires reliance on Conn. Thus, claims 8 and 39 are patentable over the asserted combination of references.

Claims 9-13 have been rejected as unpatentable under 35 U.S.C. § 103(a) over Goldman in view of Sinofsky, Dew and Makower. These claims recite the use of a thermal sensor to maintain a

desired temperature. Makower discloses the use of infrared sensing to control heating of prostate tissue during the treatment of benign prostate hypoplasia. What is significant is that Makower does not cure any of the deficiencies in the attempted combination of Goldman with Sinofsky and Dew. Furthermore, once again, it is only an attempt re reconstruct applicants' invention which prompts citation of Makower. There is nothing in the remaining references to suggest that use of a temperature sensor is needed or desirable. The rejection of these claims is thus in error.

Claims 14-17 and 20-23 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Makower in combination with Roth and Dew. None of these references have anything to do with treatment of varicose veins. Makower and Roth are both directed to treatment of BPH and Roth discloses, at column 10, line 33, that the standard wavelength for an Nd:YAG laser is 1,064 nm. Makower discloses a Nd:YAG laser, but gives no information with regard to wavelength, so it is reasonable to read Makower as disclosing a standard Nd:YAG laser having a wavelength of 1064 nm. The notion that one skilled in the art interested in treating BPH as disclosed in Makower and Roth which explicitly or implicitly disclose the standard wavelength of 1,064 nm would have any interest in the secondary laser wavelength of Dew et al., which is used for an entirely different purpose, is simply untenable. Furthermore, Makower and Roth cannot be combined. Makower is directed to a device which has a "locking" means to prevent movement of his laser and all of the claims in Makower are limited to a locking means. Roth, on the other hand, wants to pull his laser device through the tissue which is incompatible with the locking system of Makower. Thus, this rejection is based on an absolutely improper combination of references. Furthermore, Dew et al. use a tuned Nd:YAG laser in order change it from its standard 1,064 nm wavelength to obtain the "secondary wavelength" of 1,320 nm for a use completely different from the treatment of BPH. See

col. 6, lines 11-18. There is absolutely nothing to suggest that either Makower or Roth would want to use the wavelength of Dew et al.

Claim 19 has been rejected under 35 U.S.C. § 103(a) as unpatentable over Makower in view of Dew, Roth and Conn. This is, if it is possible, an even more improper combination than that of Makower, Dew and Roth. Conn teaches a diffusing tip for a laser. There is nothing in any of Makower, Dew or Roth to suggest that they have any interest in a diffusing tip, that it would be useful in any of their devices or that one skilled in the art would have any inclination to use a diffusing tip in those devices. Thus, this rejection is also in error.

It is believed that the foregoing discussion establishes the reversibility of the Examiner's rejections. However, there is much more. Applicants have submitted several declarations during the course of prosecution which trace the real-world evolution of the treatment of varicose veins with energy and have pointed out the Navarro Patent No. 6,398,777 and its place in the evolution of varicose vein technology. We turn now to those considerations.

Navarro Patent No. 6,398,777

The Navarro patent is regarded by those in the art as representative of the early work done with regard to the use of lasers in treating varicose veins. It discloses the use of lasers which have wavelengths in the range of 500-1100 nm which target the hemoglobin in blood as a chromophore for these wavelengths.

The Adoption of Laser Technology

Prior to the present invention, all of the laser devices for patient treatment of varicose veins used lasers having wavelengths in the range of 810-980 nm. As shown in Exhibits A-E to the Hennings Declaration dated June 30, 2005, these devices were:

Exhibit A – Dorniter – 940 nm

Exhibit B – Biolitac – 980 nm

Exhibit C – AngioDynamics – 980 nm

Exhibit D – Vascular Solutions – 810 nm, 940 nm and 980 nm

Exhibit E – Diomed – 810 nm

Thus, the real world of laser treatment of varicose veins prior to the present invention constituted targeting hemoglobin as a chromophore and using wavelengths in the range of 810-980 nm. This is reflected in a survey article entitled *Endovenous laser ablation: mechanism of action* by Drs. Fan and Rox-Anderson which is attached as Exhibit 1 to the second Hennings Declaration dated December 22, 2008.

The Fan/Rox-Anderson article also describes, at page 208, the difference between the Navarro and other prior art wavelengths and that of the present invention as follows:

> "Hemoglobin and to a lesser extent myoglobin in vein wall smooth muscle components are the dominant chromophores at the lower end of this range [810, 940, 980 and 1064 nm], while at 1320 nm water dominates as the energy-absorbing molecule."

At page 209, the Fan/Rox-Anderson article describes the use of 1320 nm energy as follows:

> "Special consideration must be given to EVLA (endovenous laser ablation) with 1320 nm Nd:YAG laser. At this wavelength the dominant chromophore is water and, as the biological tissue is largely composed of water, deeper energy penetrance and photothermolytic effect can be achieved at lower fluence. Compared with 12-15 W power setting typically used during EVLA with 810-1064 nm wavelength light, EVLA at 5 W with the 1320 nm laser has been shown to be effective at 12-month follow-up for closing saphenous veins 12mm in diameter. At this higher wavelength and lower energy application, clinical evidence of perforation (pain, bruising) appears to be reduced."

Prior Art Taught Against the Use of Wavelengths Higher Than 1064 nm

At the time the present invention was made, it was the prevailing scientific view that the use of laser wavelengths above 1064 nm was undesirable. In addition to the fact that hemoglobin would no longer be a chromophore for wavelengths above 1064 nm, it was believed that, as reflected in Exhibits A, B and C to the Geriak Declaration dated November 22, 2005 that it would be disadvantageous to the patient to use wavelengths higher than 1064 nm.

As stated in the Minn et al. article, Exhibit A to the Geriak Declaration entitled *Endovenous Laser Treatment of Saphenous Vein Reflux: Long-Term Results* from the Journal of Vascular and Interventional Radiology, August 2003, pages 991-996, at page 995:

> "Published experience with endovenous laser with use of wavelengths other than 810 nm is limited. A recent study by Chang and Chua reported the use of 1064 nm laser energy delivered endovenously for treatment of GSV (greater saphenous vein) reflux. Although this study reported a success rate of 96.8% in 244 legs followed up to 28 months, significant complications were noted, including paresthesias (36.5%) and skin burns (4.8%).... In addition, patients treated with the 1064 nm wavelength underwent spinal or general anesthesia rather than strictly local tumescent anesthesia."

Thus, as the wavelength increased, additional "significant complications were noted" and, unlike treatment with lower wavelengths, spinal or general anesthesia was required rather than strictly local anesthesia.

Still further, at page 995, the Minn et al. article goes on to state:

> "In comparison, in our series of more than 500 limbs treated with 810 nm diode laser energy delivered endovenously, there have no heat related complications despite the high temperatures attained at the laser fiber tip. This may be explained by the following: (1) improved delivery and use of sufficient amounts of tumescent fluid in the proper tissue plane providing protective thermal 'sync'; (2) selected homogeneous and circumferential heating of the inner vein wall by absorption of 810 nm laser energy by blood lining the vein wall, as noted in a recent study by Proebstle et al., rather than deeper penetration of laser energy as

> less homogeneous heating from endovenous laser performed with wavelengths such as 1064 nm which are absorbed less by blood and more by water; and (3) faster rates of withdrawal and shallower depth of penetration of 810 nm laser energy resulting in less damage to surrounding nontarget tissue compared with methods that use RF."

The Proebstle article referred to in the Minn et al. article is Exhibit B to the Geriak Declaration and is entitled *Thermal Damage of the Inner Vein Wall During Endovenous Laser Treatment: Key Role of Energy Absorption by Intravascular Blood*, which appeared in Dermatologic Surgery, July 2002, pages 596-600. This article, e.g., at page 599, plainly teaches the desirability of using laser energy in the range 810-980 nm, e.g., at page 599, where it emphasizes that blood plays a "key role in absorption of 940 nm laser energy but also in absorption of 810 and 980 nm laser energy". Thus, the emphasis was on using wavelengths for which blood, not water, would be a chromophore.

Similarly, the Proebstle article attached to the Geriak Declaration as Exhibit C, which is entitled *Endovenous Treatment of the Greater Saphenous Vein With a 940 nm Diode Laser: Thrombotic Occlusion After Endoluminal Thermal Damage by Laser-Generated Steam Bubbles*, which appeared in Journal of Vascular Surgery, April 2002, pages 729-736, emphasizes the then prevailing view that it was important to target blood as the chromophore with a 940 nm wavelength laser.

The foregoing articles are, of course, consistent with the disclosure in the Navarro '777 patent. In addition, each of them cites to the Navarro article which appeared in Dermatological Surgery in 2001 in Volume 27 at pages 117-122 as the initial work in using lasers to treat varicose veins which was the basis for the Navarro '777 patent. These references are footnote 12 in Exhibit A

to the Geriak Declaration, footnote 3 in Exhibit B and footnote 8 in Exhibit C. This Navarro paper contains essentially the same disclosure as the Navarro '777 patent.

Thus, to recapitulate prior to the present invention, not only was blood (and the hemoglobin in blood) considered to be the proper choice of chromophore for treatment of varicose veins with laser wavelengths in the range 810-980 nm, but it was also the view of the prior art that treatment with wavelengths as high as 1064 nm was undesirable. This is confirmed by the 2008 survey article by Fan/Rox-Anderson which cites the Navarro '777 patent in footnote 15 as the earliest disclosure of laser treatment of varicose veins. Thus, the uniform view expressed in the scientific literature is that, prior to the present invention, there was no consideration of using anything other than blood as a chromophore for laser energy in the 810-980 nm wavelength range, and that a wavelength as high as 1064 nm was undesirable. The present invention was a substantial and significant departure from this prior art, i.e., targeting water as a chromophore with laser energy in the range 1200-1800 nm was demonstrably unobvious to the prior art.

Furthermore, subsequent to applicants' invention, at least one other worker has followed in their footsteps. *See* Paithankar, Published Application No. 2005/001523, filed June 30, 2004, based on a provisional application filed on June 30, 2003, which discloses the use of wavelength of 1160 nm to 2600 nm in the treatment of varicose veins. Paithankar confirms, in paragraphs 53 and 54, that using energy having the wavelengths claimed in the present application minimizes collateral damage to "tissues surrounding the target blood vessel."

The Examiner's Refusal to Consider the Evidence of Patentability

The Examiner has repeatedly refused to consider the evidence of patentability submitted by applicants. In the earlier final rejection dated February 12, 2007, the Examiner had the following to

say about the scientific literature and the activity of those in the real world of varicose vein treatment:

> "Applicant then posits that in the real world those attempting to use lasers 'to accomplish the purpose of Goldman' deliberately choose not to use applicants wavelengths. The examiner must respectfully disagree. Firstly, it is noted that the three articles submitted by applicants do not constitute a statistically significant sample of all the publications dealing with laser treatment of varicose veins and as such, cannot be the basis for a claim such as made by applicant. Secondly, the 'purpose of Goldman' is to heat the vessel wall {see, for example column 9, line 13}. The purposes of the articles submitted by applicant is (sic) is to heat the blood in the vessel. And, as clearly taught by Dew et al. and set forth above, this is achieved by employing wavelengths that are absorbed by the tissue that it is desired to be heated."

In the final rejection dated March 13, 2009, the Examiner seems to abandon the position taken in the final rejection dated February 12, 2007 and says the following with regard to the evidence of patentability:

> "It is important to note that the articles and product information were submitted with affidavits and that all affidavits only aver that the submissions are "true copies" of the articles or product literature which is described in the affidavits. There is no assertion whatsoever in any affidavit of record that the articles or product literature are in any way representative of the prior art with respect to varicose vein treatment. Instead such assertion are made only in the remarks accompanying the affidavits. This is interesting, given that these remarks bear the signature of Mr. Geriak one of the affiants. However, as these assertions are only submitted in the form of remarks accompanying a response, they cannot be elevated to the status of evidence. As such, these remarks are noted, but do not speak to the propriety of the combination which the examiner has applied to the claims."

The foregoing statement is remarkable in many respects, but the single most remarkable aspect of the Examiner's statement is the sentence which says "There is no assertion whatsoever in any affidavit of record that the articles or product literature are in any way representative of the prior art with respect to varicose vein treatment." Just the opposite is true.

In the Hennings Declaration dated December 22, 2008, after stating in paragraph 4 that Mr. Hennings has "30 years of experience in the design, development and use of laser-based devices for medical applications and 6 years of such experience with regard to lasers used for treatment of varicose veins", Mr. Hennings says, in paragraph 10:

> "Based on my own first-hand knowledge I can state unequivocally that the Examiner was incorrect in refusing, at page 11 of the Examiner's answer, to accept the assertions of our counsel, Mr. Geriak, that Exhibits A, B and C to his declaration were representative of the prior art. Furthermore, I believe that the Fan/Rox-Anderson article attached hereto is fully consistent with the fact that Exhibits A, B and C attached to the aforesaid Geriak declaration are representative of the prior art."

Similarly, in paragraph 8 of the Goldman Declaration dated December 23, 2008, Dr. Goldman states:

> "Our use of laser wavelengths in the range 1200-1800 nm as claimed in the present application was contrary to the view held by prior art workers that such wavelengths would be undesirable, a view expressed in the Minn and Proebstle articles which are attached to the Geriak declaration as Exhibits A, B and C and which are representative of the belief held by the prior art prior to the invention claimed in this application."

Thus, the Examiner's assertion that there are no such declarations of record in the present application is profoundly erroneous.

The Examiner's earlier statement in the final rejection dated February 12, 2007 that the articles attached as Exhibits A, B and C to the Geriak Declaration do not constitute a "statistically significant sample" of "all the publications dealing with laser treatment of varicose veins" is not only seriously misguided and unsupported by identification of any other such publications, it is also at odds with the Fan/Rox-Anderson survey article attached as Exhibit 1 to the Hennings Declaration dated December 22, 2008. That article cites to the two Proebstle articles, Exhibits B and C to the Geriak Declaration, in footnotes 7 and 14. This is a powerful demonstration that the Proebstle

articles are fully representative of the prior art. In addition, the Fan/Rox-Anderson article also cites two articles from the Journal of Vascular and Interventional Radiology in footnotes, 12, 21 and 22 which is the same journal in which the Minn article attached as Exhibit A to the Geriak Declaration appeared. There are no articles cited in the Fan/Rox-Anderson survey article which in any way contradict or express a view contrary to the view expressed in Exhibits A, B and C to the Geriak Declaration. Thus, there is absolutely no basis for the notion that those articles are "not statistically significant". Furthermore, from a statistics perspective, if all of the articles on a given subject agree, they are indeed statistically significant.

In addition, the Examiner's position statement at pages 19 and 20 of the final rejection dated March 13, 2009 takes on a surreal quality when compared with the Examiner's statement at page 2 of that final rejection that "In paragraph 6, declarant (Hennings) asserts that the scientific literature attached to the Geriak declaration 'are fully representative of the prior art with respect to varicose vein treatment." And the Examiner's statement at page 4 that "In paragraph 10, declarant (Hennings) asserts that 'I can state unequivocally that the Examiner was incorrect in refusing, at page 11 (sic 9) of the Examiner's answer, to accept the assertions of our counsel, Mr. Geriak, that Exhibits A, B and C to his Declaration were representative of the prior art.'" is equally at odds with his position statement on pages 19 and 20. Thus, although the existence of any such declarations is denied on page 19 of the final rejection, there is a recognition on pages 2 and 4 that such declaration statements do exist. Then, to compound matters, the Examiner goes on to say at page 4 of the final rejection that "Declarant's (Hennings) statement is simply opinion testimony." Factual statements such as those made by Mr. Hennings cannot be blithely wished away by characterizing them as "opinion". The Hennings statements are fact, not opinion, and are not contradicted by anything in the record.

Indeed, the Examiner acknowledges at pages 5 and 6 that the Fan/Rox-Anderson article is consistent with the articles which are exhibits to the Geriak Declaration being representative of the prior art.

Furthermore, at page 8 of the final rejection, the Examiner discusses paragraph 8 of the Goldman Declaration but entirely fails to recognize the statement in that paragraph that Exhibits A, B and C to the Geriak Declaration are representative of the prior art.

Thus, the Examiner has variously denied the existence of the Hennings and Goldman Declarations (page 19), recognized the statements in paragraphs 6 and 10 of the Hennings Declaration at pages 2 and 4 of the final rejection, but dismissed them as "simply opinion testimony" at page 4 of the final rejection and has ignored the same statement regarding representative prior art in paragraph 8 of the Goldman Declaration at page 8 of the final rejection. This head-spinning inconsistency in the final rejection defies explanation.

Thus, the final rejection falls far short of the standard set forth in In Re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006) that:

> "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead there most be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."

Here, there is just the opposite. The Examiner's statement of his positions is inconsistent and those positions are all over the lot. Furthermore, those positions cannot be read other than as a flat-out refusal to give effect to the evidence of patentability submitted by the applicants. Such a refusal is directly contrary to law as set forth in In Re Sullivan, 498 F.3d 1345, 84 USPQ2d 1034 (Fed. Cir. 2007) which held that evidence submitted by a patent applicant must be given meaningful consideration. Furthermore, as noted in In Re Sullivan, at 498 F.3d 1351, evidence "that the prior art teaches away from the claimed invention in any material respect is probative evidence of

unobviousness." Similarly, the decisions in In Re Haruna, 249 F.3d 1327, 1335 (Fed. Cir. 2001) and in Tec Air, Inc. v. Denso Mfg. Co., 192 F.3d 1353, 1360 (Fed. Cir. 1999) state that:

> "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, ... would be led in a direction divergent from the path that was taken by the applicant."

This is precisely the situation presented in this appeal in which the applicants diverged both with regard to chromophore targets and laser wavelengths from the path taken by the prior art. This is compelling rebuttal evidence of patentability. However, the Examiner has utterly failed to comply with the requirement of Sullivan at 498 F.3d 1351 that:

> "When a patent applicant puts forth rebuttal evidence, the Board must consider that evidence. *See* In Re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995.)"

In Sullivan, the Court remanded the case to the Board. In the present case, it is respectfully submitted that the deficiencies in the Examiner's rejections, even without his refusal to consider the evidence of patentability set forth in the declarations, mandate a reversal of the Examiner's rejections and that the evidence of patentability which has been submitted would overwhelmingly refute a prima facie showing of obviousness if such a showing had been made. Thus, it is believed that reversal of the Examiner's rejections is appropriate.

Conclusion

The claims in the present application are directed to an invention which is plainly patentable over the prior art. It is respectfully submitted that a reversal of each of the rejections is appropriate.

Request for Oral Hearing

Applicant hereby requests that an Oral Hearing be scheduled in this application. The Commissioner is hereby authorized to charge any fees associated to Deposit Account No. 15-0665.

Fees

The Commissioner is authorized to charge Orrick's Deposit Account No. **15-0665** for any fees required and credit any overpayments to said Deposit Account No. **15-0665**.

Respectfully submitted,

Orrick, Herrington & Sutcliffe, LLP

Dated: September 11, 2009 By: 

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APPENDIX 1

APPENDIX

1. An endovenous method of treating a varicose veins comprising the step of using a laser having a wavelength between about 1.2 and about 1.8 um to heat and shrink collagen in a varicosed vein and to destroy the functionality of the varicose vein.

2. The method of claim 1 in which the laser energy is delivered with a fiber optic laser delivery device.

3. The method of claim 1 further comprising the following steps:

inserting a fiber optic laser delivery device into the varicose vein;

using a pullback device to retract the fiber optic laser delivery device through the varicose vein at a rate of between about 0.1 mm/sec and about 10.0 mm/sec while simultaneously delivering laser energy therefrom.

4. The method of claim 3 in which the fiber optic laser delivery device is retracted at a rate of between about 1.0 mm/sec and about 5.0 mm/sec.

5. The method of claim 3 in which the pullback device begins retraction of the fiber optic laser delivery device just prior to initiating delivery of the laser energy, thereby preventing the tip of the fiber, optic laser delivery device from sticking to the vessel wall.

6. The method of claim 1 further comprising the preliminary step of removing blood from the varicosed vein prior to treatment with laser energy.

7. The method of claim 2 in which the fiber optic laser delivery device is introduced to the varicose vein through an introducer catheter.

8. The method of claim 2 in which the energy delivered through the fiber optic laser delivery device is evenly distributed by using a diffuse radiating-tip mounted to the distal end of the fiber optic laser delivery device.

9. The method of claim 2 in which an non-contact thermal sensor is used to maintain a desired temperature.

10. The method of claim 9 in which the thermal sensor is used to maintain a desired coagulation temperature.

11. The method of claim 9 in which the thermal sensor is used to maintain a desired collagen shrinkage temperature.

12. The method of claim 2 further comprising the step of using the fiber optic laser delivery device as a thermal sensing element.

13. The method of claim 9 further comprising the step of modulating the laser power based on the sensed temperature to maintain the desired temperature.

14. A system for endovenous treatment of varicose veins comprising the following:

a laser having a wavelength between about 1.2 and about 1.8 um; and

a fiber optic laser delivery device having a proximal end and a distal end, for delivery of laser energy from the distal end of the fiber optic laser delivery device to the inside wall of a varicose vein wherein the functionality of the varicose vein is destroyed and collagen in the varicosed vessel wall can be heated and shrunk.

15. The system of claim 14 further comprising a pullback device which retracts the fiber optic laser delivery device through the varicose vein at a rate of between about 0.1 mm/sec and about 10.0 mm/sec.

16. The system of claim 14 further comprising means for administration of anesthesia to tissue surrounding the varicose vein, wherein the anesthesia causes swelling of the tissue surrounding the varicose vein which causes compression of the varicose vein in order to remove blood prior to treatment.

17. The system of claim 14 further comprising an introducer catheter in which an elongated lumen portion has a proximal end and a distal end, wherein the fiber optic laser delivery device is introduced to the introducer catheter through the proximal end and is introduced to the varicose vein through the distal end.

18. (cancelled)

19. The system of claim 17 further comprising a diffusing tip at the distal end of the introducer catheter for providing even distribution of energy radiating during treatment.

20. The system of claim 17 further comprising a diffusing tip at the distal end of the fiber optic laser delivery device for providing even distribution of energy radiating during treatment.

21. The system of claim 14 further comprising an non-contact thermal sensor.

22. The system of claim 21 further comprising a controller coupled to the thermal sensor for controlling the temperature in a region near the distal end of the fiber optic laser delivery device.

23. The system of claim 22 in which the controller modulates a power input to the laser for controlling the temperature in a region near the distal end of the fiber optic laser delivery device.

24. (cancelled)

25. An endovenous method of treating varicose veins with laser energy to heat and shrink collagen in the vein and to destroy the functionality of the varicosed vein, the method comprising the following steps:

inserting a laser delivery device into the varicose vein;

delivering laser energy having a wavelength between about 1.2 and about 1.8 um to the varicose vein; and

retracting the laser delivery device through the varicose vein, thereby heating and shrinking the collagen in the vein and destroying the functionality of the varicose vein.

26. The method of claim 1 wherein the laser has a wavelength of about 1.32 um.

27. The system of claim 14 wherein the laser has a wavelength of 1.32 um.

28. The method of claim 25 wherein the laser energy has a wavelength of about 1.32. um.

29. The method of claim 1 wherein said laser is a Nd:YAG laser.

30. The system of claim 14 wherein said laser is a Nd:YAG laser.

31. The method of claim 25 wherein said laser is a Nd:YAG laser.

32. The method of claim 1 wherein the laser energy preferentially heats the water in the wall of the vein.

33. The system of claim 14 wherein the laser is adapted to preferentially heat water.

34. The method of claim 25 wherein the laser energy preferentially heats the water in the wall of the vein.

35. A method of treating varicose veins, comprising:

providing a beam of light comprising a wave length in the range of about 1200 nm to about 1800 nm; and

delivering endovascularly the beam of light to target a chromophore comprising water in the wall of a targeted varicose vein to treat the vein.

36. (Cancelled)

37. The method of claim 1 wherein said wave length is about 1320 nm.

38. The method of claim 35 further comprising delivering the beam of light via an optical fiber.

39. The method of claim 38 further comprising delivering the beam of light through a diffusing tip connectable to the optical fiber.

40. The method of claim 35 wherein the treatment comprises reducing the size of the targeted varicose vein.

41. The method of claim 1 further comprising heating the target chromophore to a temperature not greater than about 85° C.

42. (previously presented) The method of claim 38 wherein a pull-back device is used to position the optical fiber.

43. The method of claim 42 wherein the pull-back device withdraws the optical fiber from the targeted varicose vein at a rate of between about 0.1 mm/sec. and about 10.0 mm/sec.

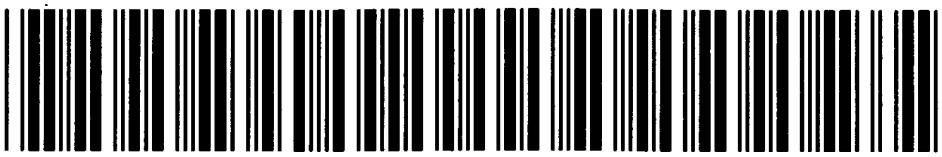
44. The method of claim 35 in which blood is removed from the varicose vein prior to treatment with the beam of light.

45. The method of claim 35 wherein the beam of light has a power between about 1 to about 20 watts.

46. The method of claim 45 wherein the beam of light has a power of about 5 watts.

APPENDIX 2

IDS REFERENCES



☐ FOR

Endovenous Laser Treatment of Saphenous Vein Reflux: Long-Term Results

Robert J. Min, MD, Neil Khilnani, MD, and Steven E. Zimmet, MD

PURPOSE: To report long-term follow-up results of endovenous laser treatment for great saphenous vein (GSV) reflux caused by saphenofemoral junction (SFJ) incompetence.

MATERIALS AND METHODS: Four hundred ninety-nine GSVs in 423 subjects with varicose veins were treated over a 3-year period with 810-nm diode laser energy delivered percutaneously into the GSV via a 600-μm fiber. Tumescent anesthesia (100–200 mL of 0.2% lidocaine) was delivered perivenously under ultrasound (US) guidance. Patients were evaluated clinically and with duplex US at 1 week, 1 month, 3 months, 6 months, 1 year, and yearly thereafter to assess treatment efficacy and adverse reactions. Compression sclerotherapy was performed in nearly all patients at follow-up for treatment of associated tributary varicose veins and secondary telangiectasia.

RESULTS: Successful occlusion of the GSV, defined as absence of flow on color Doppler imaging, was noted in 490 of 499 GSVs (98.2%) after initial treatment. One hundred thirteen of 121 limbs (93.4%) followed for 2 years have remained closed, with the treated portions of the GSVs not visible on duplex imaging. Of note, all recurrences have occurred before 9 months, with the majority noted before 3 months. Bruising was noted in 24% of patients and tightness along the course of the treated vein was present in 90% of limbs. There have been no skin burns, paresthesias, or cases of deep vein thrombosis.

CONCLUSIONS: Long-term results available in 499 limbs treated with endovenous laser demonstrate a recurrence rate of less than 7% at 2-year follow-up. These results are comparable or superior to those reported for the other options available for treatment of GSV reflux, including surgery, US-guided sclerotherapy, and radiofrequency ablation. Endovenous laser appears to offer these benefits with lower rates of complication and avoidance of general anesthesia.

J Vasc Interv Radiol 2003; 14:991–996

Abbreviations: GSV = great saphenous vein, RF = radiofrequency, SFJ = saphenofemoral junction

LOWER-extremity venous insufficiency is a common medical condition afflicting 25% of women and 15% of men in the United States (1). Gender, pregnancy, hormones, aging, and gravitational forces from prolonged standing or sitting are the most common factors that influence the appearance or worsening of primary varicose veins (2,3). Although many people seek medical treatment for varicose veins because they find them unsightly, most people with varicose veins do experience symptoms (4,5). Unfortunately, symptoms of primary venous insufficiency are often not recognized by patients or their physicians. Characteristic leg complaints associated with varicose veins include aching pain, night cramps, fatigue, heaviness, or restlessness. Symptoms arise from pressure on somatic nerves by dilated veins and are typically worsened with prolonged standing, during the premenstrual period, or in warm weather (6). Left untreated, nearly 50% of patients with significant superficial venous insufficiency will eventually experience chronic venous insufficiency characterized by lower-extremity swelling, eczema, pigmentation, hemorrhage, and ulceration (7).

Great saphenous vein (GSV) reflux is the most common underlying cause of significant varicose veins. Traditional treatment of GSV reflux has been surgical removal of the GSV. Al-

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R.J.M. is a consultant to Diomed (Andover, MA), assisting in development of medical treatments and physician training. R.J.M. is coinventor and part owner of a patent on endovenous laser treatment of veins, for which he receives royalties. R.J.M. and Cornell Vascular have paid for all medical equipment used in procedures relating to this study. S.E.Z. is a paid consultant to Diomed, Inc. (Andover, MA), assisting in development of medical treatments. S.E.Z. is also paid to assist in physican training. S.E.Z. purchased all medical equipment he used in connection with this study. The other author has not identified a potential conflict of interest.

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though surgical ligation and stripping of the GSV has been the most durable treatment, it is associated with significant perioperative morbidity. Less-invasive surgical treatments including high ligation of the GSV at the saphenofemoral junction (SFJ) have been attempted with the hope that gravitational reflux would be controlled while the vein is preserved for possible use as a bypass graft. Unfortunately, ligation of the GSV alone usually results in recurrent varicose veins (8). Even when high ligation has been combined with phlebectomy of varicose tributaries or retrograde sclerotherapy, recurrence has been the rule (9,10). Therefore, when it is determined that GSV reflux is the principal underlying problem, treatment should involve eliminating this source of reflux with ablation of any associated incompetent venous segments.

In 1999, Boné (11) first reported on delivery of endoluminal laser energy. Since then, a method for treating the entire incompetent GSV segment has been described (12,13). Endovenous laser treatment, which received approval from the US Food and Drug Administration in January 2002, allows delivery of laser energy directly into the blood vessel lumen. Nonthrombotic vein occlusion is accomplished by heating the vein wall with 810-nm-wavelength laser energy delivered via a 600-μm laser fiber (Diomed, Andover, MA). Sufficient heating of the vein wall is necessary to cause collagen contraction and denudation of endothelium. This stimulates vein wall thickening, eventual luminal contraction, and fibrosis of the vein. The purpose of this study is to report on the long-term follow-up results of endovenous laser treatment for GSV reflux.

MATERIALS AND METHODS

This prospective, nonrandomized, consecutive-enrollment study included 423 patients who underwent endovenous laser treatment of incompetent GSV segments with 810-nm diode laser energy delivered intraluminally for treatment of primary varicose veins. The study protocol was approved by the Weill Medical College of Cornell University Institutional Review Board. All patients gave written informed consent before treatment.

Patient Selection

Directed history and physical examination, including duplex ultrasound (US) evaluation of the superficial venous system, was performed on limbs of subjects with varicose veins. Study inclusion criteria included varicose veins caused by SFJ incompetence with GSV reflux as demonstrated by duplex US imaging, age of at least 18 years, and ability to return for scheduled follow-up examinations for 12 months after endovenous laser treatment. Exclusion criteria included nonpalpable pedal pulses; inability to ambulate; deep vein thrombosis; general poor health; pregnancy, nursing, or plans to become pregnant during the course of participation in the investigation; and extremely tortuous GSVs that would not allow endovenous catheterization and passage of the laser fiber as identified on pretreatment venous duplex US mapping. After initial consultation and evaluation, subjects meeting the appropriate criteria were offered surgery versus endovenous laser treatment. Nearly all subjects chose endovenous laser over surgical ligation and stripping.

Five hundred four incompetent GSVs were treated with endovenous laser over a 39-month period. Five limbs were lost to follow-up. The remaining 499 limbs in 423 patients comprise the study population. This group consists of 352 women (83%) and 71 men (17%) ranging in age from 23 to 72 years, with a mean age of 42 years.

Follow-up ranged from 1 month to 39 months with a mean follow-up period of 17 months and an SD of 11 months. Aching leg pain was the most common presenting symptom, found in 87% of limbs. Overall, slightly more left legs (n = 263, 53%) were treated, and 76 patients (18%) were treated for bilateral GSV reflux. Pretreatment GSV diameter, measured in the upright position approximately 2 cm below the SFJ, ranged from 4.4 mm to 29 mm (mean, 11 mm; SD, 4.2 mm).

None of the patients in this series underwent concomitant ambulatory phlebectomy. All but seven patients underwent compression sclerotherapy treatment of distal varicose tributaries or associated telangiectasias at follow-up visits.

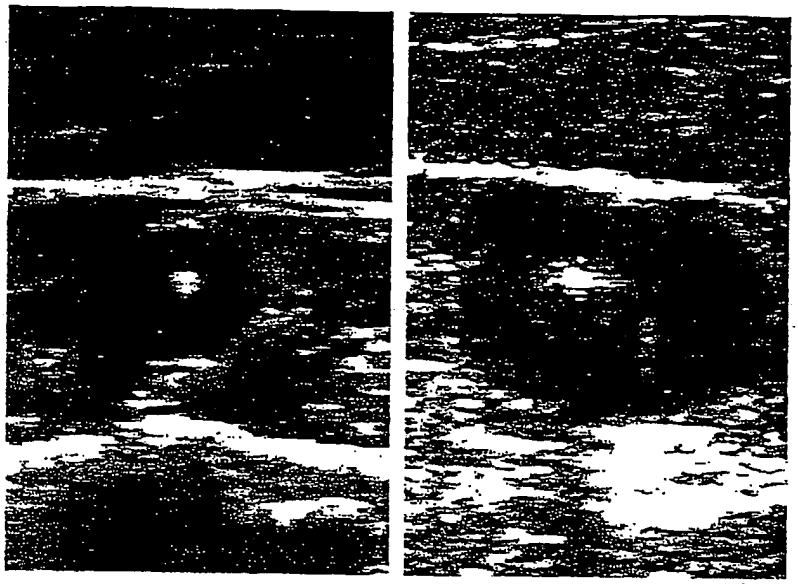
Description of Technique

Duplex US was performed in the upright position to map incompetent sources of venous reflux and then to mark the skin overlying the incompetent portion of the GSV starting at the SFJ. After venous duplex mapping, a percutaneous entry point was chosen. This point may be where reflux is no longer seen or where the GSV becomes too small to access (usually just above or below knee level). With use of local anesthesia and sonographic guidance, the GSV was punctured. A 5-F introducer sheath was placed into the GSV over a guide wire and advanced past the SFJ into the femoral vein. Intraluminal position within the GSV was confirmed by aspiration of nonpulsatile venous blood and visualization with US.

The sheath was flushed and a 600-μm laser fiber (Diomed) was inserted in the sheath and advanced up to the first site mark, indicating that the distal tip of the laser fiber was flush with the end of the sheath. The sheath was then withdrawn to the second site mark, exposing the distal 3 cm of the bare-tipped laser fiber. The sheath and fiber were pulled back together and positioned at the SFJ under US guidance. Position was confirmed by direct visualization of the red aiming beam of the laser fiber through the skin.

Tumescent local anesthesia consisting of 100–200 mL of 0.2% lidocaine neutralized with sodium bicarbonate, was administered along the perivenous space with use of US guidance. In addition to the anesthetic effects, properly delivered, this fluid serves two important functions: (1) it compresses and reduces the diameter of even the largest veins to provide vein wall apposition around the fiber tip with subsequent circumferential heating of the vein wall and (2) it provides a "heat sink" to minimize the possibility of heat-related damage to adjacent tissues. Figure 1a demonstrates the typical transverse sonographic appearance of the laser fiber and catheter seen centrally within an enlarged GSV located in the saphenous space. Proper and adequate delivery of tumescent anesthesia should result in fluid surrounding a compressed GSV as shown in Figure 1b.

The tip of the laser fiber was repo-



a. b.

Figure 1. Duplex US (transverse view) demonstrating appearance of the GSV before and after proper delivery of tumescent anesthesia. (a) Intraluminal position of laser fiber and catheter within an enlarged GSV; (b) tumescent anesthesia delivered by echogenic needle tip adjacent to laser fiber and catheter with fluid surrounding the compressed GSV.

sitioned within the GSV 5–10 mm distal to the SFJ. Tip position was checked by US and direct visualization of the red aiming beam through the skin. Laser energy (810-nm diode laser; Diomed) was delivered at 14 W in continuous mode. The vein was treated from 5–10 mm below the SFJ to approximately 1 cm above the skin entry site. Length of GSV treated with endovenous laser ranged from 10 cm to 55 cm (mean, 35 cm; SD, 10 cm). The laser fiber was withdrawn at an average rate of 3 mm per second (18 cm per minute). Of patients treated with 14-W continuous mode (n = 276, or 55% of limbs), delivery of laser energy ranged from 25 seconds (at 358 J) to 187 seconds (at 2,615 J), with a mean of 123 seconds (SD, 47 sec) or 1,727 J (SD, 650 J).

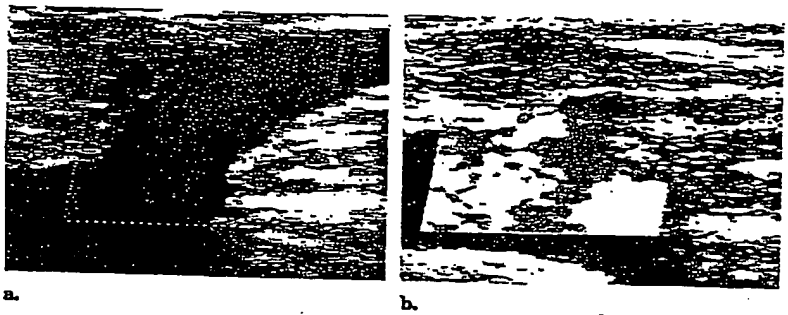
A class II (30–40 mm Hg) full-thigh graduated support stocking or panty hose was worn for at least 1 week at all times except to sleep or to shower. Patients were instructed to ambulate and resume their normal daily activities immediately. Clinical and duplex US follow-up was obtained at 1 week, 1, 3, 6, 9, and 12 months, and then yearly.

Compression sclerotherapy treatment of distal varicose tributaries was performed with use of sodium tetradecyl sulfate (0.3%–1% concentration). A detailed description of sclerotherapy technique is beyond the scope of this article but the approach used was the "French school" originally advocated by Tournay and more recently popularized in the United States by Goldman and other phlebologists (14). This technique relies on starting from the highest points of reflux and proceeding downward, and treating veins from the largest to the smallest. Compression stockings or panty hose were worn for at least 1 week after sclerotherapy treatments except to sleep or shower. Sclerotherapy treatments were performed at 4-week intervals, starting 1 month after endovenous laser ablation of the GSV.

Study Endpoints and Definitions

Duplex US criteria for successful treatment were the following: at 1-week follow-up, an enlarged noncompressible GSV, minimally decreased in diameter, with echogenic, thickened vein walls, and no flow seen within the occluded vein lumen on color Doppler interrogation; at 3- and 6-month follow-up, an occluded GSV with substantial (>50%) reduction in diameter; and at 1 year and beyond, complete disappearance of the GSV or minimal residual fibrous cord with no flow detectable. It is important to note that the expected appearance 1–2 weeks after endovenous laser is a slightly smaller GSV demonstrating wall thickening with absence of flow within the treated vein segment. The vein lumen is usually obliterated by the thickened wall, which has low-level echoes and is incompressible. This wall thickening should be differentiated from acute GSV thrombosis wherein the vein is also incompressible but the lumen is filled with anechoic acute thrombus. Several weeks after successful endovenous laser treatment, resolution of the acute inflammation in the vein wall should result in reduction in vein diameter. After several months, most of the treated vein segments will fibrose and be difficult to identify. Alternatively, superficial thrombophlebitis with GSV thrombus would result in recanalization of the vein. A longitudinal view of an enlarged, incompetent GSV is seen in Figure 2a. Figure 2b demonstrates the typical color Doppler appearance of a successfully treated GSV 1 year after endovenous laser treatment.

Clinical evaluation was performed on all subjects at 1 week, 1, 3, 6, 9, and 12 months, and yearly thereafter by the same physician (R.M.) who performed all the endovenous laser procedures. Patients were queried about symptomatic relief at follow-up visits, particularly improvement or resolution of lower-extremity pain believed to be associated with venous insufficiency. Improvement in the appearance of the leg, including reduction in visible varicosities, swelling, pigmentation, or other skin changes secondary to chronic venous insufficiency, were assessed by the patient and with direct comparison with pretreatment photographs obtained from all subjects undergoing treatment. Patients were evaluated for possible adverse reactions caused by endovenous laser treatment at each follow-up visit. Minor complications were defined as those that had no significant clinical sequelae, such as bruising. Major complications were defined as those necessitating an increased level of care, sur-



a. b.

Figure 2. Color Doppler examinations (longitudinal views) of the GSV at the SFJ demonstrating successful occlusion after endovenous laser treatment. (a) Pretreatment evaluation demonstrates an enlarged GSV with reflux after distal calf compression; (b) 1-year follow-up examination shows typical "cul-de-sac" appearance of the proximal GSV with occlusion of the treated segment.

gery, hospitalization, or permanent adverse sequelae.

RESULTS

Follow-up results ranging from 1 month to 39 months (mean, 17 months; SD, 11 months) were obtained in 499 of the 504 limbs treated with endovenous laser during the study period. Successful endovenous laser treatment, as defined earlier, was seen in 490 of 499 limbs (98%) at 1-month follow-up. Eight of nine GSVs requiring repeat endovenous laser were successfully closed with a second endovenous laser treatment. Continued closure of the treated GSV segments was noted at longitudinal follow-up at the following rates: 444 of 447 (99.3%) at 3 months, 390 of 396 (98.5%) at 6 months, 351 of 359 (97.8%) at 9 months, 310 of 318 (97.5%) at 1 year, and 113 of 121 (93.4%) at 2 years. Forty subjects have been followed for 3 years and no new recurrences were seen at 2 or 3 years that were not present at 1-year follow-up. In fact, all recurrences were noted before 9 months, with the majority seen by 3 months. This may indicate that these were not true recurrences but rather inadequate initial treatments.

Clinical examination correlated well with duplex US findings. All patients showed improvement in the appearance of the limb with disappearance or reduction in the size and number of visible varicosities. The typical appearance of varicose veins caused by incompetence of the SFJ with GSV reflux is shown in Figure 3a. One month after endovenous laser treatment, relief of symptoms and significant improvement in the appearance of the varicose veins was noted (Fig 3b). By 6 months after initial treatment, pain was greatly improved or resolved in all treated limbs. Although symptomatic resolution and significant improvement in the appearance of the leg is usually noted after endovenous laser treatment alone, most patients will need additional complementary procedures (ie, sclerotherapy or phlebectomy) to fully realize the restorative benefits of treatment.

Bruising outside the puncture site was noted in 24% of limbs at 1-week follow-up. Bruising resolved in all subjects before 1-month follow-up. Ninety percent of subjects felt a delayed tightness peaking 4–7 days after laser treatment and lasting 3–10 days. This sensation, described as "pulling" along the course of the treated GSV, was not felt in the nine patients in whom initial treatment failed. Five percent of patients developed superficial phlebitis of varicose tributaries after endovenous laser occlusion of the GSV. Most cases required no treatment. Symptomatic patients were treated with graduated compression stockings and over-the-counter antiinflammatory agents. All minor complications listed earlier resolved without sequelae. There have been no skin burns, paresthesias, cases of deep vein thrombosis, or other minor or major complications. The procedure was well-tolerated by all subjects with strictly local anesthesia.

Overall treatment satisfaction was determined by asking subjects if they would recommend the procedure to a friend with similar leg vein problems, and 422 of 423 subjects (99.8%) indicated they would recommend the procedure.

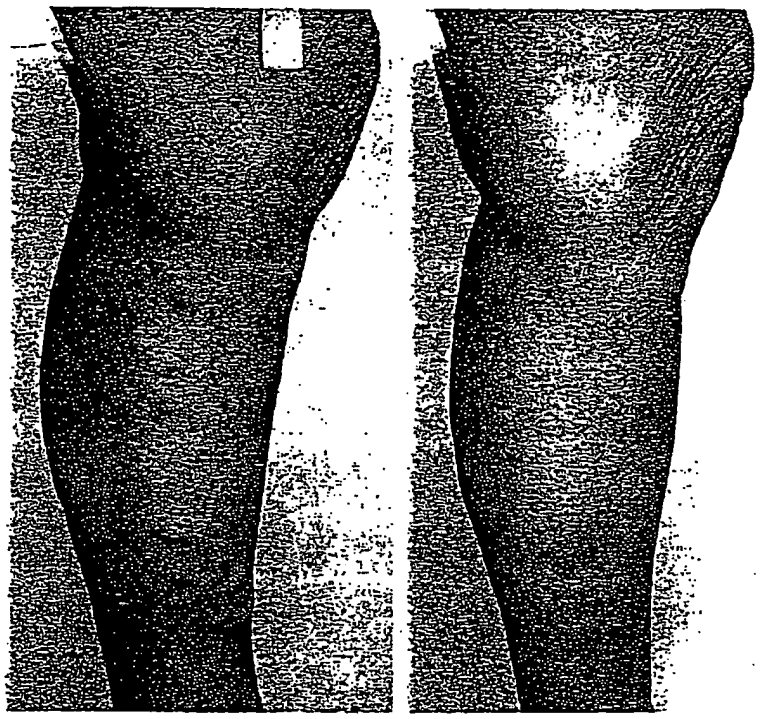
DISCUSSION

Percutaneous methods for treating incompetent GSVs are not new. Duplex-guided sclerotherapy for treatment of GSV reflux has been attempted, but long-term studies have failed to prove durability comparable to surgery (15–19). Initial attempts at damaging vein walls by electrocoagulation involved creation of a thrombus within the vessel lumen, ultimately resulting in recanalization (20–22). Early methods of intraluminal delivery of high-frequency alternating-current radiofrequency (RF) energy to treat GSV reflux were complicated by skin burns, saphenous nerve and peroneal nerve injury, phlebitis, and wound infection (23).

A more modern technique of the use of RF energy to eliminate saphenous vein reflux has been developed by VNUS Medical Technologies (Sunnyvale, CA). Early results reported from a multicenter trial demonstrated a reasonable degree of success with an overall failure rate of 10% at a mean follow-up of 4.7 months (13% in patients treated with RF alone and 5% in patients treated with RF plus high ligation of the GSV). Complications included transient paresthesias (thigh, 9%; leg, 51%), skin burns (3%), deep venous thrombosis (3%), and one pulmonary embolus (24). More recent studies have demonstrated success rates of 73%–90% with follow-up to 24 months in 21 limbs (25–27).

One of the limitations of our study is that it does not provide a blinded, randomized comparison of the various modern percutaneous methods available for treatment of GSV reflux, including RF and wavelengths of laser energy other than 810 nm. However, review of the literature allows some comparisons and raises some interesting areas for future study.

RF current damages tissue by resistive heating of structures in direct con-



a. b.

Figure 3. Significant improvement in appearance of varicose tributaries after endovenous laser treatment of an incompetent left GSV. (a) Typical appearance of varicose veins caused by GSV reflux; (b) the same leg 1 month after endovenous laser treatment.

tact with the electrodes. Deeper tissue planes are heated by conduction into normothermic tissue. Because the potential for heating of adjacent perivenous tissue is high, safe treatment with RF depends on proper delivery of adequate tumescent anesthesia. Effective use of tumescent anesthesia appears to have reduced the incidence of heat-related complications. In expert hands, the incidence of paresthesias after RF has occurred in as few as 8.5% of limbs within 1 week of treatment and decreased to 0.7% at 6 months (27). However, with less-experienced physicians, RF still has been complicated with heat-related adverse effects such as paresthesias (10% at 6 months) and skin burns (3.3%) (25).

Published experience with endovenous laser with use of wavelengths other than 810 nm is limited. A recent study by Chang and Chua (28) reported the use of 1,064-nm laser energy delivered endovenously for treatment of GSV reflux. Although this study reported a success rate of 96.8% in 244 legs followed up to 28 months, significant complications were noted, including paresthesias (36.5%) and skin burns (4.8%). In addition to endovenous laser ablation, all patients in their study underwent surgical ligation and division of the proximal and distal ends of the treated GSV. In addition, patients treated with the 1,064-nm wavelength underwent spinal or general anesthesia rather than strictly local tumescent anesthesia (28).

In comparison, in our series of more than 500 limbs treated with 810-nm diode laser energy delivered endovenously, there have been no heat-related complications despite the high temperatures attained at the laser fiber tip. This may be explained by the following: (1) improved delivery and use of sufficient amounts of tumescent fluid in the proper tissue plane providing a protective thermal "sink;" (2) selective, homogeneous, and circumferential heating of the inner vein wall by absorption of 810-nm laser energy by blood lining the vein wall, as noted in a recent study by Proebstle et al (29), rather than deeper penetration of laser energy and less-homogeneous heating from endovenous laser performed with wavelengths such as 1,064 nm, which are absorbed less by blood and more by water; and (3) faster rates of withdrawal and shallower depth of penetration of 810-nm laser energy, resulting in less damage to surrounding nontarget tissue compared with methods that use RF.

It has been suggested that a randomized controlled trial comparing outcomes of endovenous laser ablation of the saphenous vein to surgical ligation and stripping should be performed; however, such a study would be difficult given patients' overwhelming desire for minimally invasive treatments rather than surgery. Review of the existing surgical literature does provide some insight in assessing treatment durability. Multiple studies have shown that recurrence of varicose veins after GSV stripping occurs early (30), with 73% of limbs destined for recurrent varicosities at 5 years already having them at 1 year (31,32). Our results with endovenous laser have supported this, demonstrating that what is found on duplex imaging early is predictive of what will be seen later, with none of the treated patients developing recanalization of successfully occluded GSVs at 2 or 3 years that was not seen before 9 months.

Performing endovenous ablation of the GSV without dissection of the SFJ violates a cardinal rule in saphenous vein surgery that each of the tributaries must be individually divided. Surprisingly, the combined experiences with transcatheter endovenous ablation procedures have shown lower recurrence rates than with surgical ligation and stripping. Perhaps minimizing dissection in the groin and preserving venous drainage in normal, competent tributaries while removing only the abnormal refluxing segments does not incite neovascularization.

The understanding of venous disorders continues to improve with tremendous strides being made over the past decade. Readily available noninvasive diagnostic tests allow physicians to precisely map out abnormal venous pathways and identify sources of incompetence. Modern percutaneous methods of sealing incompetent veins

provide patients with alternatives to ligation and stripping for treatment of GSV reflux without the familiar morbidities associated with surgery (33,34). Given these recent advances, many physicians, when properly trained, will now be able to successfully diagnose and treat the whole spectrum of superficial venous insufficiency, offering acceptable options to the millions of people in the United States alone who have varicose veins but are unwilling or unable to undergo surgery.

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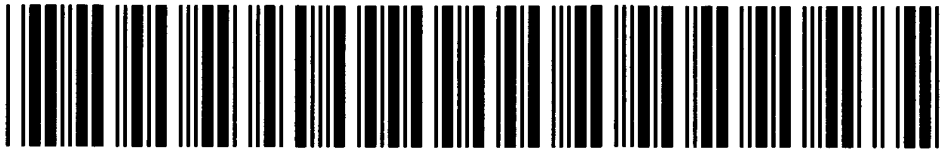

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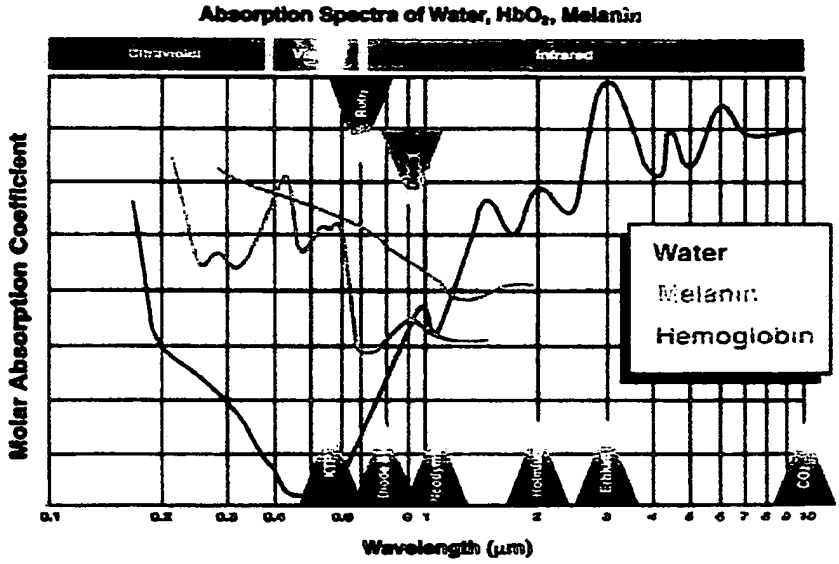
The Dornier **D940 Laser** Wavelength



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- Deep penetration
- Optimal absorption characteristics for hemoglobin (3x more than an 810 or 1064 nm laser)
- Optimal absorption characteristics for water (*10x more than an 810 nm laser, and 3x more than a 1064 nm laser*)
- Minimal melanin absorption when compared to other lasers (*3x less than an 810 nm laser, which enables treatment of darker skin-types*)

These absorption characteristics result in a safer and more effective treatment for both spider and varicose veins.

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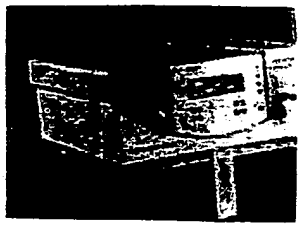
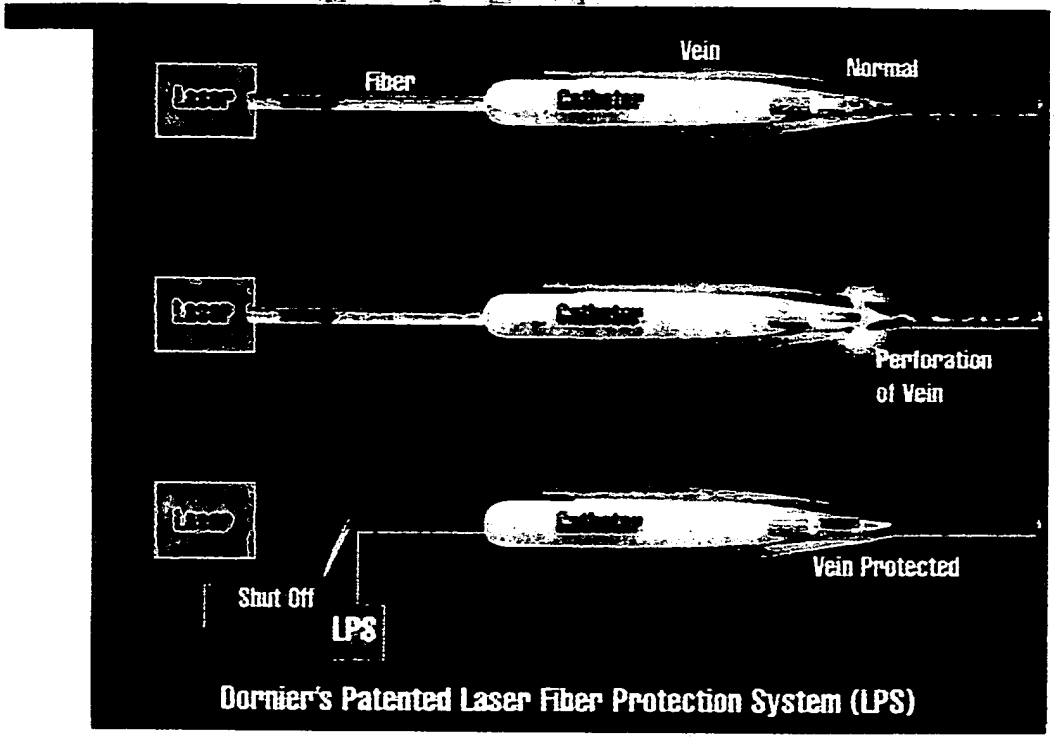


The Dornier D940



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Normal Operation
A normal fiber tip achieving optimal results on vein tissue layers.

No LPS Feedback
Fiber tip starts to char, absorbing laser light and producing unwanted damaging heat.

LPS Feedback
Tip has charred, triggering feedback and the LPS shut off for protection.

Technical Data

Wavelength
940 nm

Laser Power at Tissue
Pulse mode: 120 w
Continuous wave: 1-60 w

Aiming Beam
Red aiming beam standard
(Green beam option for better visibility)
Power 0-150mW adjustable

Laser Transmission System
Lightguides core diameter 600µm
Lightguide connector: SMA modified

Application Modes
Pulse: removal of unwanted hair, vascular treatment
Standard: coagulation/ablation
Fiberoptic contact cutting
ZOLF interstitial coagulation

Pulse Mode
Pulse energy: up to 10J
Pulse duration: 10-100 ms
Pulse interval: 200 ms-2 s
or Pulse repetition: up to 5 Hz

Record
Simultaneous display of applied energy, irradiation time and number of pulses

Power Supply
100-240 V, 50/60 Hz, 1.3 KVA

Dimensions (HxWxD) 8"x19"x20"

Weight
55 pounds

Standards/Classifications
IEC 601, IEC 825 European medical device directive Device protection class I, BF
Laser class IV

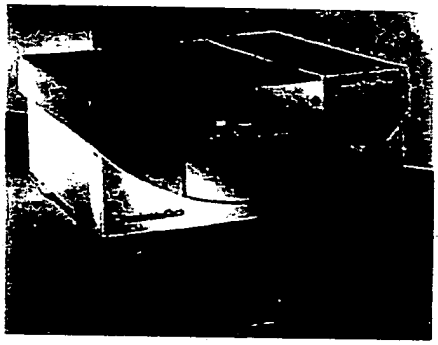
The Dornier D940 laser sets a new standard for any aesthetic laser center or physician in practice.

About Dornier MedTech ...
Specializing in lithotripters, orthopedic shock wave devices, urotables and medical lasers, Dornier *MedTech* has operating units and service partners throughout the world - and continues to maintain its commitment to the medical device industry by providing innovative therapeutic, diagnostic and service solutions for numerous medical fields.

"The Dornier 940 nm laser is the most effective to date for the treatment of spider veins. This same laser will also replace stripping in 85% of patients who have saphenous vein insufficiency."

Ron Rush, MD, FACS
Midwest Vein Treatment Clinic

Dornier MedTech Americas



The highly unique light of a 940 nm wavelength ensures precise targeting of vessels because of its:

- Deep penetration
- Optimal absorption characteristics for hemoglobin (5x more than an 810 or 1064 nm laser)
- Optimal absorption characteristics for water (10x more than an 810 nm laser, and 3x more than a 1064 nm laser)
- Minimal melanin absorption when compared to other lasers (3x less than an 810 nm laser, which enables treatment of darker skin-types)

These absorption characteristics result in a safer and more effective treatment for both spider and varicose veins

Dornier D940 Diode Laser System

Dornier specifically chose the 940 nm wavelength to design the D940 diode laser system for the treatment of superficial veins, as well as saphenous vein insufficiency.

The Dornier D940 is the first and only laser to emit light at 940 nm and is engineered with the newest PowerBar® technology to provide high peak powers from a small package.

Weighing only 55 pounds, the Dornier D940 is lightweight and easily transportable, with a retractable handle and built-in wheels. Plugs into any 110-volt outlet and is backed by Dornier's nation-wide service organization.

Close Window

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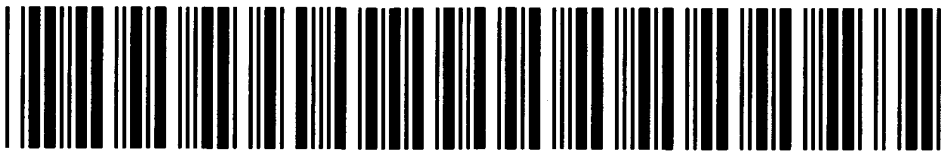

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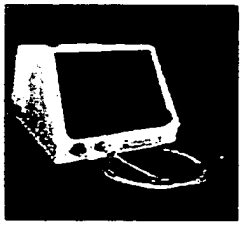
980nm Diode Laser Series



biolitec's 980nm Diode Laser Series, including the Ceralas D and SmilePro 980 Lasers, are ideal for soft-tissue applications in medical, dental, and veterinary environments.

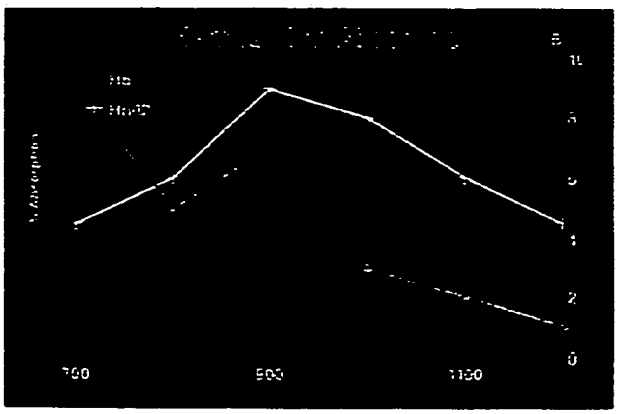
With unsurpassed, optimal absorption in water and hemoglobin, the 980 nm laser series allow controlled tissue ablation and provide a bloodless field for most surgical procedures. Unlike other medical lasers, **biolitec**'s 980nm lasers cut and coagulate optically — with negligible collateral tissue damage, charring, and recession. Many procedures using the 980nm lasers are pain-free, minimizing or even eliminating the need for anesthesia. These state-of-the-art 980nm lasers are compact and portable at 15 pounds and require no special cooling or maintenance.

More information about the SmilePro 980 for Dentistry.

More information about the Ceralas D for medical applications.

ELVeS™ – Endo Laser Vein System

ELVeS is a revolutionary new minimally-invasive laser treatment for superficial reflux of the greater saphenous vein - which may lead to varicose veins. Progressing the capabilities of vein treatments, ELVeS takes about 45 minutes and only local anesthesia is used - allowing patients to walk home after treatment! With virtually instant relief from venous reflux, patients can return to their normal lifestyle and activities immediately following treatment.



Other Laser Wavelengths

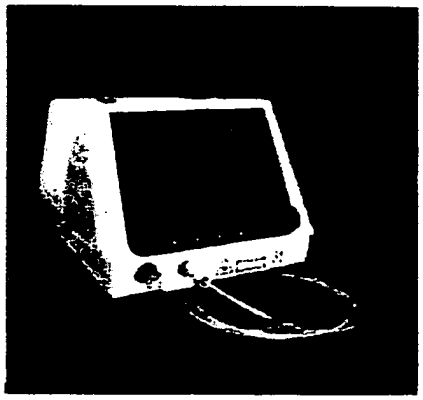
Other lasers' wavelengths are either absorbed too much or too little in water and / or hemoglobin and are consequently limited in several ways.

The 810 nm lasers' energy is eight times *less* absorbed in water than the 980 nm wavelength. Therefore, 810 nm lasers' fibers require 'conditioning' because their wavelengths can not properly ablate tissue. The conditioned tip of these lasers' fibers needs to heat up in order to work. In addition, the light energy from these lasers is absorbed in their fibers' tips – not in water, hemoglobin, or tissue. The laser light never reaches the patient - only the heat via a 'hot tip.'

Conductive heat is the only means of cutting and coagulating with lasers that require conditioned tips - which can damage collateral tissue and cause swelling, excessive necrosis, and patient discomfort.

The 980 nm Wavelength

A major benefit of the Ceralas D 980 nm Laser's unique wavelength is the ability to operate optically - *not via a 'hot tip.'* Because hemoglobin and water absorb the 980 nm wavelength at an optimal rate, the fiber tips of the Ceralas D laser do not require conditioning.



Because the Ceralas D exhibits superior control and minimizes collateral tissue damage, it is one of the most valuable and versatile lasers available today. "Although the 810 nm diode laser has been used for endovenous treatment, I feel it is not the best wavelength, as it does not absorb well in water," says John Mauriello, MD, a phlebologist in private group practice with offices in Charlotte and Durham, North Carolina. "The 940 nm diode laser is better than the 810 nm because it is on the up-slope of the water absorption curve. **But my research convinces me that 980 nm is the perfect wavelength because it is right on the peak of the water absorption curve.**"

ELVeS FAQs

The ELVeS Procedure

Advantages of **biolitec**'s Endo Laser Vein System for Doctors

More information for Patients

Attend a *King-Size* ELVeS Seminar!

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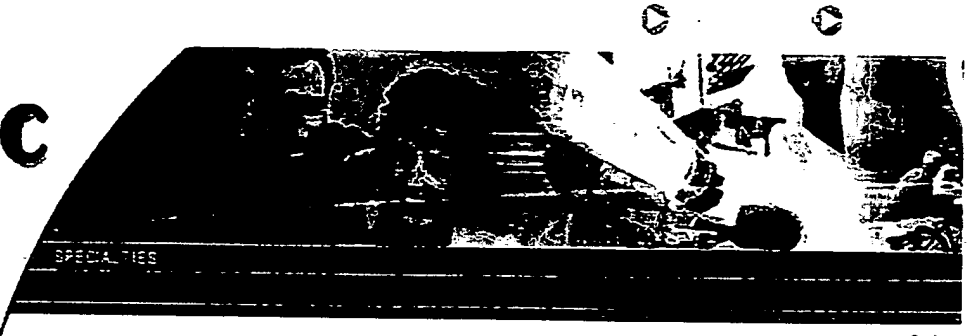
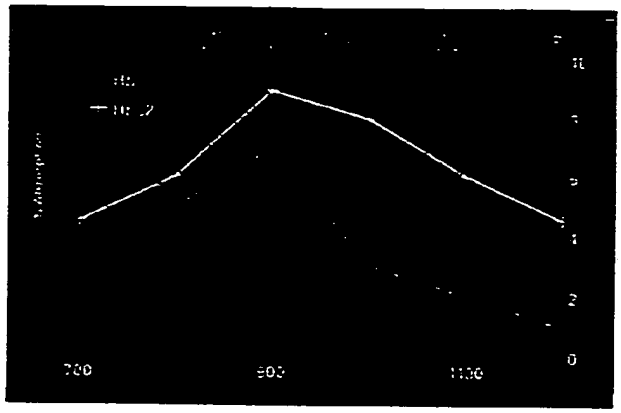
Investors | Patient Information | Contact Us

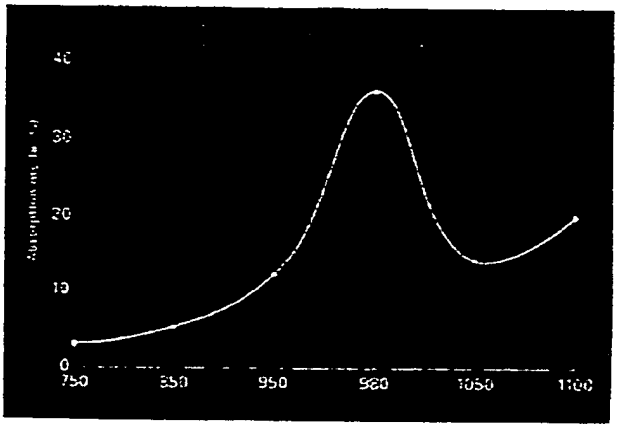


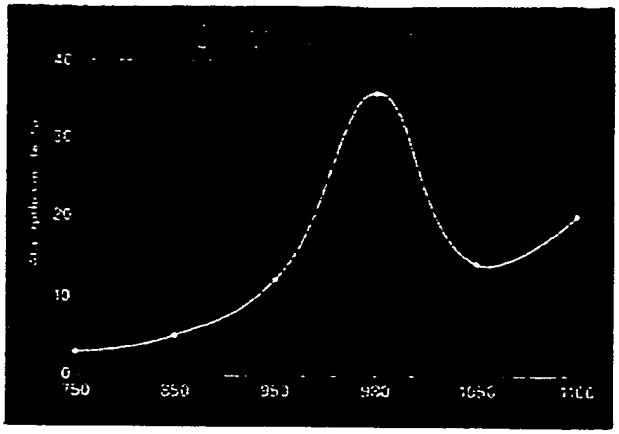
The Importance of a Laser's Wavelength: Advantages of 980 nm

A laser's wavelength determines many of its properties and capabilities. As a result of **biolitec's** extensive research in photobiology and laser physics, we have developed a series of 980 nm lasers that exhibit unparalleled lasing effects.

Since soft tissue contains a high percentage of water and hemoglobin, a laser's light energy must be well absorbed in both to cut and coagulate optimally. Considering the absorption characteristics of water and hemoglobin together, 980 nm is the ideal wavelength for soft tissue applications - including the ELVes Treatment for superficial reflux of the GSV, which often leads to varicose veins.







SmilePro 980 Technical Specifications

Laser Type	Integrated GaAlAs semiconductor laser arrays
Wavelength	980 nm
Output power	15 Watts
Power Range	1 - 15 W
Output power increments	1 Watt
Operating modes	Continuous or Pulsed
Pulse duration in On or Off modes	0.01 to 99.9 seconds
Aiming beam	Visible semiconductor (635 nm, red) < mW
Cooling	Air cooled
Weight	15 lbs
Dimensions	7" x 9" x 14" (h x w x d)
Power requirement	110 / 220 V

Ceralas D Technical Specifications

Laser Type	Integrated GaAlAs semiconductor laser arrays
Wavelength	980 nm
Output power	15 W, 25 W, 50 W
Power Range	1 - 15 W, 1 - 25 W, 1 - 50 W
Output power increments	1 Watt
Operating modes	Continuous or Pulsed
Pulse duration in On or Off modes	0.01 to 99.9 seconds
Aiming beam	Visible semiconductor (635 nm, red) < mW
Cooling	Air cooled
Weight	14 lbs (15 W, 25 W); 19 lbs (50 W)
Dimensions	7" x 9" x 14" (15 W, 25 W); 7" x 15" x 16" (50 W)
Power requirement	110 / 220 V

For more information, contact your local sales representative or send an email to us at info@biolitec.com.

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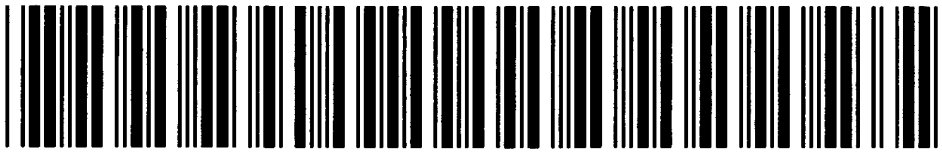

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Thermal Damage of the Inner Vein Wall During Endovenous Laser Treatment: Key Role of Energy Absorption by Intravascular Blood

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*Department of Dermatology and §Institute of Pathology, University of Mainz, Germany, †Clinic for Dermatologic Surgery, Linz, Austria, and ‡Dornier MedTech Laser GmbH, Wessling, Germany

BACKGROUND. Despite the clinical efficacy of endovenous laser treatment (EVLT), its mode of action is incompletely understood.

OBJECTIVE. To evaluate the role of intravascular blood for the effective transfer of thermal damage to the vein wall through absorption of laser energy.

METHODS. Laser energy (15 J/pulse, 940 nm) was endovenously administered to explanted greater saphenous vein (GSV) segments filled with blood ($n = 5$) or normal saline ($n = 5$) in addition to GSVs under in vivo conditions immediately prior to stripping. Histopathology was performed on serial sections to examine specific patterns of damage. Furthermore, in vitro generation of steam bubbles by different diode lasers (810, 940, and 980 nm) was examined in saline, plasma, and hemolytic blood.

RESULTS. In saline-filled veins, EVLT-induced vessel wall injury was confined to the site of direct laser impact. In contrast, blood-filled veins exhibited thermal damage in more remote areas including the vein wall opposite to the laser impact. Steam bubbles were generated in hemolytic blood by all three lasers, while no bubbles could be produced in normal saline or plasma.

CONCLUSION. Intravascular blood plays a key role for homogeneously distributed thermal damage of the inner vein wall during EVLT.

W. ROTHER, PHD WAS AN EMPLOYEE OF DORNIER MEDTECH LASER GMBH. THE STUDY WAS SUPPORTED BY DORNIER MEDTECH LASER, WESSLING, GERMANY, AND BIOLITEC, JENA, GERMANY. T. M. PROEBSTLE, MD, MSC, M. SANDHOFER, MD, A. KARGL, MD, D. GÜL, MD, J. KNOP, MD, PHD, AND H. A. LEHR, MD, PHD HAVE INDICATED NO SIGNIFICANT INTEREST WITH COMMERCIAL SUPPORTERS.

RECENTLY, MINIMALLY invasive techniques have been clinically introduced for the effective treatment of varicose veins. In particular, VNUS closure[1,2] and endovenous laser treatment (EVLT)[3–5] have been shown to abolish reflux in the incompetent greater saphenous vein (GSV). Short-term efficacy has been reported as greater than 90%[1,2] and 95%,[3–5] respectively, comparing well with the results of classic surgery including high ligation and stripping of the GSV.[2] However, while the mode of action of VNUS closure has been studied in detail, the mechanisms of EVLT action are still not completely understood. It has been shown that EVLT, unlike VNUS, does not lead to occlusion of the vein by significant shrinkage of the vessel wall,[6] but instead causes a thrombotic occlusion of the laser-treated vein.[5]

Histopathologic examination of laser-treated veins revealed perforation of the vein wall at the site of direct laser impact and thermal damage of adjacent vein wall areas.[5,6] For the latter effect, laser-induced steam bubble formation has been postulated as the responsible mechanism,[5] implicating a putative role for intravascular blood serving as a chromophore absorbing the laser energy. In order, to further clarify the role of intravascular blood during EVLT, we performed comparative in vitro and in vivo experiments in the presence or absence of intravascular blood.

Patients and Methods

Administration of Laser Energy to GSV Samples

EVLT was applied as previously described in detail.[5] In brief, a 600 μm bare fiber with an outer diameter of 1.00 mm was connected to a 940 nm diode laser. Under in vivo conditions (see Patients), the fiber was inserted below the knee into the surgically exposed GSV. The fiber was advanced proximally to the point of high ligation of the GSV and subsequently withdrawn in steps of about 3–5 mm while

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laser energy was applied.[5] Identical laser parameters were chosen for the in vitro experiments with GSVs (see below).

In Vitro Experiments With GSVs

After classic varicose vein surgery of the GSV under tumescent local anesthesia,[7,8] the stripped vein segment was transferred to a saline bath at room temperature. The veins were cut into pieces 10 cm in length, and each piece was ligated at the proximal end before the laser fiber was inserted from the distal end. The vein was then filled either with heparinized blood (500 IU heparin/20 ml of blood) or with normal saline. After the distal end was ligated tightly around the laser fiber, single laser pulses of 15 J (15 W, 1 second) were delivered every 3–5 mm during stepwise withdrawal of the fiber tip. During the entire procedure the vein was bathed completely in normal saline solution. A total of 10 specimens, 5 filled with blood and 5 filled with normal saline during treatment, were subsequently fixed in formaldehyde, embedded in 1 mm rings in paraffin blocks, and studied histologically in routine hematoxylin and eosin stains on serial 5 µm sections. Each section was evaluated with respect to signs of thermal damage at the site of direct laser impact, at the adjacent area, and at more distant sites. Particular attention was given to the vein wall opposing the site of direct laser impact.

Patients

Two patients scheduled for classic varicose vein surgery under tumescent local anesthesia[7] consented to undergo experimental EVLT in the interval between high ligation and stripping of the GSV. One patient received EVLT with a blood-filled GSV. In the second patient, conditions were identical, apart from the fact that blood was washed out of the GSV and replaced by normal saline prior to EVLT. Complete replacement of blood by saline solution was confirmed visually by a flexible vascular fiberscope. The time interval between EVLT and invaginated stripping was 15 minutes. The vein was then cut into 2 cm sections, fixed in formaldehyde, and embedded in paraffin blocks for later histologic examination.

Laser-Generated Steam Bubbles in Normal Saline, Plasma, or Hemolytic Blood

An in vitro setup to measure laser-generated steam bubble sizes was used as previously described.[5] Diode lasers with 810 nm, 940 nm, and 980 nm were used with appropriate 600 µm fibers as provided by the manufacturers. Before starting the comparative experiments, the energy output of each device was calibrated at the fiber tip with a power meter. Before each experiment, the fiber tips were freshly cut to avoid secondary carbonization effects. Each laser wavelength was tested in tubes filled with normal saline, human plasma, and hemolytic blood by administration of pulses between 3 and 16 J. Plasma was obtained by centrifugation of heparinized blood for 20 minutes at 2000 g. Hemolytic blood was produced by replacing the removed plasma with equal volumes of distilled water.

Results

EVLT was performed under in vitro conditions on GSV segments either filled with blood ($n = 5$) or filled with normal saline ($n = 5$). In addition, EVLT was performed in vivo after high ligation but before stripping of the GSV, in a vessel filled with either blood or normal saline. The generation of steam bubbles in normal saline, plasma, and hemolytic blood was examined for laser wavelengths of 810, 940, and 980 nm under in vitro conditions.

Pathologic Examination of GSV Segments Receiving In Vitro EVLT

A minimum of 20 hematoxylin and eosin-stained serial sections of each vein segment were examined microscopically. Detectable changes of the vein wall, attributable to endovenous laser action, were highly reproducible. Figure 1 displays representative cross sections of laser-treated GSV segments. In saline-filled veins, vein wall damage was exclusively confined to the site of direct laser impact (Figure 1B), while adjacent regions (Figure 1A) and, in particular, the opposite side of the vein wall (Figure 1C) show virtually no signs of tissue damage. In contrast, pronounced thermal damage was detectable along the entire vein wall in blood-filled veins (Figure 1D,E), even at the vein wall opposite the laser impact (Figure 1F).

Pathologic Examination of EVLT Effects on Surgically Removed Veins

The histopathologic examination of veins stripped after EVLT under in vivo conditions showed a similar pattern of thermal damage as the veins treated under in vitro conditions described above. Figure 2 displays representative sections of laser-generated complete perforations of the vein wall produced from the saline-filled (Figure 2A,B) or blood-filled (Figure 2D,E) vein. Again, the immediate site of laser impact exhibited a comparable extent of coagulative necrosis, regardless of whether the vein contained saline (Figure 2A) or blood (Figure 2D). However, even the immediately adjacent inner vein wall showed distinct differences in the extent of thermal damage (Figure 2A,B,D,E), with severe injury in the blood-filled vein and a virtually normal situation in the saline-filled vein. Also, the vein wall located at the opposite site of the laser impact showed heat damage in the blood-filled vein (Figure

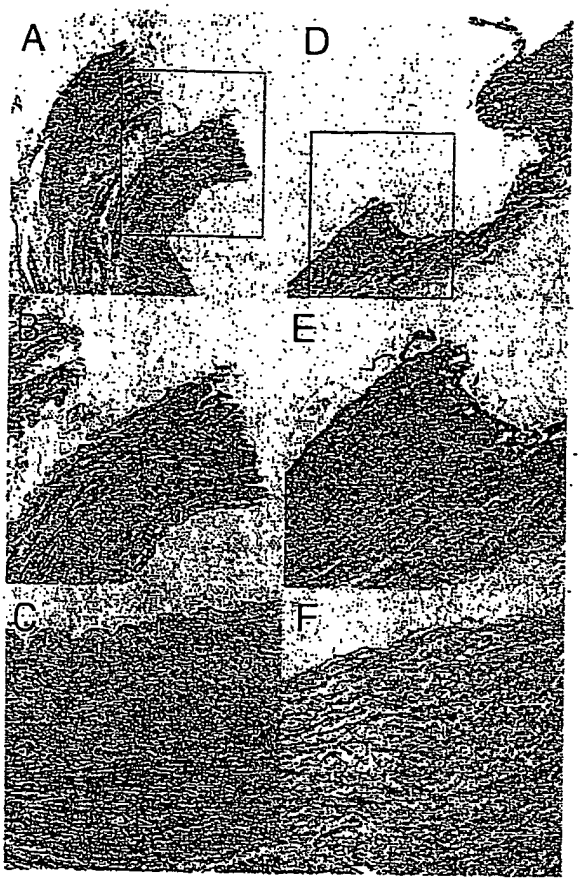

Figure 1. Representative hematoxylin and eosin sections of GSV segments after in vitro EVLT of A–C) saline filled veins or D–F) veins filled with heparinized blood. Under both conditions, direct laser impact causes perforation (A,B) or pronounced tissue ablation with focal coagulation necrosis at the immediate site of impact (D,E). In contrast to the saline-filled vein (A,B), the blood-filled vein exhibits more intensive and more remote injury to the adjacent vein wall areas (D,E). Likewise, superficial coagulative injury to endothelium, intima, and inner media are seen in vein wall areas on the opposite side of the laser impact in blood-filled veins (F), but are virtually absent in saline-filled veins (C). At most, slight tissue edema may be seen (C). Original magnification 55× (A,D) and 140× (B,C,E,F).

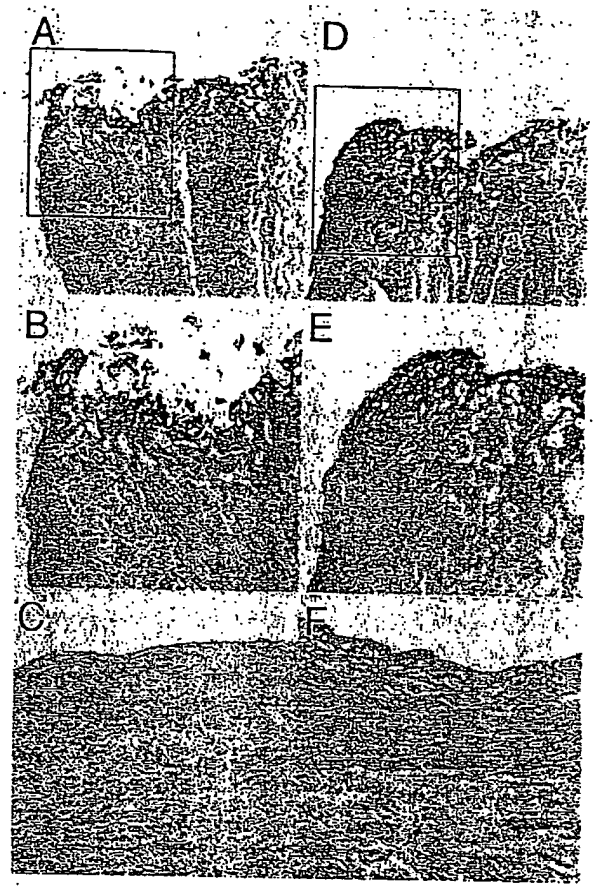

Figure 2. Histopathologic results of in vivo EVLT obtained from A–C) saline-filled or D–F) blood-filled veins. Arrangement of the panels as well as histomorphologic changes are identical to those described in Figure 1 and in the Results section of the manuscript.

2F), while in the saline-filled vein, only minimal laser-induced thermal damage was observed (Figure 2C).

Laser-Induced Steam Bubbles in Normal Saline, Plasma, and Hemolytic Blood

For laser wavelengths of 810, 940, and 980 nm, steam bubble volumes were plotted against the administered pulse energy (Figure 3). If the tube was filled with normal saline or plasma, no wavelength was able to produce detectable steam bubbles with pulse energies up to 16 J (data not shown). In contrast, in tubes filled with hemolytic blood, steam bubble sizes showed an almost linear proportionality with the administered laser energy. Note that no major difference could be detected between the three laser wavelengths. This indicates that the absorption of all three lasers by hemolytic blood is strong enough to transfer the energy completely into heat.

However, we found that this was true only if fresh-cut fiber tips were used for each experiment. Otherwise carbonization of the fiber tip led to extremely high tip temperatures, causing additional generation of energy through combustion of organic compounds of the hemolytic blood (data not shown).

Discussion

Despite growing acceptance and a rapid clinical introduction of EVLT, the underlying mechanism of action of this novel technique is still not fully understood. In a recent report of Weiss[6] it was demonstrated in elegant animal studies that endovenous radiofrequency

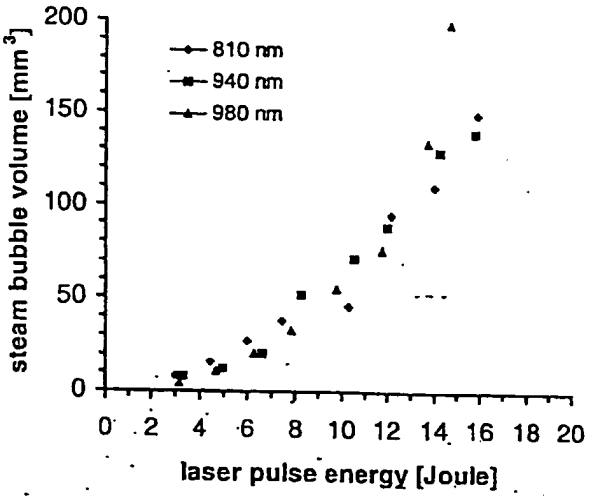

Figure 3. Laser-induced steam bubble volume in hemolytic blood plotted against delivered pulse energy for wavelengths of 810 nm (rhomboid), 940 nm (square), and 980 nm (triangle). No steam bubbles were produced with any of the experimental conditions in normal saline or plasma (data not displayed).

occlusion and EVLT have completely different modes of action. EVLT almost completely lacks the shrinkage effect of the vessels caused by prolonged exposure to moderate heat (85°C) in radiofrequency occlusion. Instead, EVLT causes perforation of the vein wall at the site of direct laser impact,[5,6] as a morphologic correlate for the consecutively observed perivenular ecchymoses.

In a previous report,[5] we proposed that laser-generated steam bubbles transfer a substantial amount of thermal damage to the vein wall during EVLT. These steam bubbles are created because of the high absorption of 940 nm laser energy in blood, with a technical penetration of only 0.3 mm. In water, this penetration depth is as much as 45 mm,[9] which is more than 100-fold deeper than in blood. Conversely, this implies that the absorption of 940 nm laser energy in water is less than 1% when compared to blood. Since under the particular topographic conditions of an endovascular laser fiber, a laser beam hits the vein wall within a markedly shorter distance than 45 mm, it can be concluded that heat generation by laser absorption cannot play a major role within a saline-filled vein. In this case, a laser beam of less than 1 mm diameter, with a fluence of more than 1500 J/cm², directly hits the vein wall, leading to complete perforating ablation of tissue (Figures 1A,B and 2A,B).

Our experimental setup tested this hypothesis under in vitro and in vivo conditions, providing histopathologic evidence: In a saline-filled vein almost the entire amount of focused laser energy is transferred to a small area at the vein wall, while in a blood-filled vein the thermal damage extends over a much wider topographic range of the inner vein wall, including the perilesional area and even areas opposite the immediate laser impact. This concordance between the in vitro and in vivo results suggests a sufficient correlation and validity of our in vitro model for the in vivo situation, despite the fact that under in vivo conditions the vein is much more compressed from outside by the presence of tumescent local anesthesia. However, one could speculate if a reduced, but still blood-filled, lumen of the vein could even facilitate laser-induced damage: relatively lower energies would suffice, because steam bubbles do not need to be generated in sizes that would be necessary to transfer homogenous damage to larger veins.

Evidence that blood plays not only a key role in absorption of 940 nm laser energy but also in absorption of 810 nm and 980 nm laser energy was provided by in vitro examination of steam bubble generation. While neither normal saline nor plasma were able to absorb laser energy substantially enough to generate steam bubbles, all three tested lasers produced comparable steam bubbles when exposed to hemolytic blood. Such steam bubbles, in all three laser systems, indicate that blood temperature passes the point of boiling at the site of the laser tip, thus transferring heat energy homogeneously to the inner vessel wall. The formation of these steam bubbles during EVLT could easily be monitored real time by duplex scanning, even allowing a continuous pullback of the laser fiber with the laser in continuous wave mode. One may speculate if with such a continuous pullback technique, perforations of the vein wall during EVLT could be avoided. However, a too-slow pullback velocity would certainly lead to a completely perforating longitudinal cut in the vein wall. Further experiments are needed on this topic. Therefore we hope that this improved knowledge about the exact mode of action of laser-induced vein damage may contribute to an improvement of endovenous laser treatment.

Acknowledgment We are grateful to Mrs. Weingärtner for skilled technical support and to Mrs. Gärtner for excellent preparation of the vein samples for histopathologic examination.

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Endovenous treatment of the greater saphenous vein with a 940-nm diode laser: Thrombotic occlusion after endoluminal thermal damage by laser-generated steam bubbles

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Purpose: Despite a rapid spread of the technique, very little is known about the laser-tissue interaction in endovenous laser treatment (EVLT). We evaluated EVLT of the incompetent greater saphenous vein (GSV) for efficacy, treatment-related adverse effects, and putative mechanisms of action.

Methods: Twenty-six patients with 31 limbs of clinical stages C_{2-6}, E_P, $A_{S,P}$, P_R with incompetent GSV proven by means of duplex scanning were selected for EVLT in an outpatient setting. A 600-μm fiber was entered into the GSV via an 18-gauge needle below the knee and proceeded to the saphenofemoral junction (SFJ). After infiltration of tumescent local anesthesia, multiple laser pulses of 15 J energy and a wavelength of 940 nm were administered along the vein in a standardized fashion. D-dimers were determined in peripheral blood samples 30 minutes after completion of EVLT in 16 patients and on postoperative day 1 in 20 patients. One GSV that was surgically removed after EVLT was examined by means of histopathology. Additionally, an experimental in vitro set-up was constructed as a means of investigating the mechanism of laser action within a blood-filled tube.

Results: A median of 80 laser pulses (range, 22-116 laser pulses) were applied along the treated veins. On days 1, 7, and 28, all limbs except one (97%) showed a thrombotically occluded GSV. In one patient, the vessel showed incomplete occlusion. The distance of the proximal end of the thrombus to the SFJ was a median 1.1 cm (range, 0.2-5.9 cm) in the remaining patients. Adverse effects in all 26 patients were ecchymoses and palpable induration along the thrombotically occluded GSV that lasted for 2 to 3 weeks. In two limbs (6%), thrombophlebitis of a varicose tributary required oral treatment with diclofenac. D-dimers in peripheral blood were tested with normal results in 14 of 16 patients 30 minutes after completion of the procedure and elevated results in 7 of 20 patients at day 1 after EVLT. However, an increase of D-dimers from day 0 to day 1 was observed in 15 of the 16 patients undergoing tests 30 minutes after EVLT and on day 1. The 940-nm laser was demonstrated by means of in vitro experiments and the histopathological examination of one explanted GSV to act by means of indirect heat damage of the inner vein wall.

Conclusion: EVLT of the GSV with a 940-nm diode laser is effective in inducing thrombotic vessel occlusion and is associated with only minor adverse effects. Laser-induced indirect local heat injury of the inner vein wall by steam bubbles originating from boiling blood is proposed as the pathophysiological mechanism of action of EVLT. (J Vasc Surg 2002; 35:729-36.)

For many patients of clinical stages C_2 to C_6 with proven incompetence of the saphenofemoral junction (SFJ) and refluxes along the greater saphenous vein (GSV), the standard surgical treatment still is high ligation of the vessel and its tributaries at the level of the SFJ, with subsequent stripping of the incompetent part of the GSV. In the last decade, less-invasive techniques have been further developed, particularly the use of tumescent local anesthesia facilitated ambulatory phlebectomy[1,2] or high ligation and stripping of the GSV.[3-5] In the last few years, a radiofrequency heating technique has been developed as an endoluminal approach with a distal, microsurgical vein access producing excellent cosmetic results.[6] One distinct major difference compared with classic varicose vein surgery is that endoluminal radio-frequency solely occludes the GSV without affecting tributaries at the level of the SFJ. Such a strategy is particularly remarkable, because it is generally accepted that recurrent varicose veins after surgery often have their origin in residual tributaries of the SFJ or in a residual saphenous stump. A recent study that suggested that, at least with short-term follow-up, extended ligation at the SFJ did not add much when compared with endoluminal closure of the GSV alone[7] raised a very controversial discussion. More recently, a similar minimally invasive technique, endovenous laser treatment (EVLT) of the GSV has been introduced,[8] and, in contrast to transcutaneous laser treatment of reticular veins and venulectasias,[9,10] we are only starting to learn about the

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Competition of interest: Dr Rother, who constructed the experimental set-up for in-vitro testing, is an employee of Dornier MedizinLaser GmbH, Germering, Germany.

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Table I. Characteristics of 31 treated limbs of 26 patients who underwent endovenous laser treatment, according to the CEAP classification

	Number of limbs(%)
Clinical stage	
C2 Varicose veins > 4 mm	31 (100)
C3 Edema	25 (81)
C4 Skin changes	11 (35)
C5 Healed ulcer	0 (0)
C6 Active ulcer	4 (13)
Etiology	
Primary	31 (100)
Secondary	0 (0)
Anatomy	
Superficial veins	31 (100)
Perforator veins	17 (55)
Cockett II/III	14 (45)
Sherman	3 (10)
Deep veins	0 (0)
Pathology	
Reflux	31 (100)
Obstruction	0 (0)

efficacy, adverse effects, and mode of action of this novel approach.

This study was conducted to obtain more detailed clinical and histopathological data on the application of EVLT in patients with clinical stages C_{2-6}, E_P, $A_{S,P}$, P_R, including an incompetent GSV. An in vitro set-up was developed and used as a means of further clarifying the mode of action of EVLT on the inner vessel wall.

METHODS

Patients. Patients were selected from our phlebology clinic as they came in for evaluation of specific complaints. As part of their routine examination, all patients underwent functional testing, including duplex scanning (Sonosite 180 plus, 4med, Erlangen, Germany). When a clinical stage C_2 to C_6 with an incompetent SFJ and reflux in the GSV were revealed by means of the phlebological examination, and thus an indication for high ligation and stripping was presented, patients were asked to choose between classic varicose vein surgery or EVLT. Only three of 29 patients preferred classic varicose vein surgery, whereas 26 patients chose EVLT. However, patients made this decision after reading information and an additional personal discussion with the physician about EVLT, which, in contrast to surgery, so far has no long-term follow-up, and the possible need for additional treatment measures, including classic surgery, later. Apart from the incompetent GSV, other incompetent superficial veins and perforator veins were tolerated, but not treated simultaneously to EVLT. Patients with secondary varicosis with deep vein reflux or deep vein obstruction were not able to undergo EVLT (Table I). All patients gave written informed consent in accordance to the Helsinki declaration.

Administration of laser energy. The whole EVLT procedure was exclusively limited to the GSV, and no additional measures like mini-phlebectomy or sclerotherapy were used as a means of treating tributaries of the GSV simultaneously. Roughly, the protocol was adapted from the paper of Navarro et al.[8] After duplex scanning-guided puncture of the GSV below the knee with an 18-gauge venous catheter (Vasofix, Braun, Melsungen, Germany), a J-tip guidewire (0.035-in, Medex Medical, Rossendale, UK) was advanced by means of duplex scanning control toward the SFJ. A 5F angio catheter (Infiniti, 100 cm, 0.97 mm, vertebral, Cordis Europe, 9301 LJ Roden, Netherlands) was shortened at the tip with a scalpel by approximately 5 cm to allow passage of the bare fiber more easily. The catheter was then forwarded over the guidewire until its tip was located approximately 1 cm distal to the SFJ. The guidewire was then removed and replaced by a 600-μm bare fiber with an outer diameter of 1.00 mm (Type D-6100-BF, Dornier MedizinLaser GmbH, Germering, Germany) connected to a 940-nm diode laser (Medilas D, Dornier MedizinLaser GmbH). With duplex scanning control, the laser fiber tip was passed through the tip of the angio catheter, thus extruding approximately 6 to 8 mm, with a final distance toward the SFJ of 1 to 2 cm. The correct location of the fiber tip could also be verified visually: in the darkened operation theater, the red (645 nm, 1 mW) pilot beam was detectable transcutaneously. Tumescent local anesthesia was then infiltrated along the GSV from the SFJ down to the point of access, as described elsewhere,[3] and given 5 minutes to establish the anesthetic effect before the start of the laser treatment. Laser energy was delivered in a pulsed fashion with a 1-second on and a 2-second off period. During the on period, 15 J of laser energy were delivered with a power of 15 W. During the off period, the fiber tip was retracted 5 to 7 mm. This cycle was repeated until a distance of 1 cm to the puncture site of the GSV was reached. In this manner, the laser treatment of the entire GSV lasted 3 to 5 minutes. Subsequently, the catheter was removed, and the patient received a full thigh class II compression stocking, resembling an ankle pressure of 30 mm Hg, and was advised to walk immediately. Additionally, as a precaution without any further rationale, low-molecular-weight heparin was administered subcutaneously for 5 days for thrombosis prophylaxis (Fragmin P, Pharmacia & Upjohn, Erlangen, Germany).

Concomitant duplex ultrasound scanning examination. All patients underwent duplex ultrasound scanning examinations before EVLT, during EVLT, and after EVLT on days 1, 7, and 28. During the course of the examinations, patients underwent scanning for refluxes in superficial veins, in the deep vein system, and also in perforating veins. Patients with an incompetent or occluded deep vein system were excluded from EVLT. Concomitant incompetent perforator veins or pathological findings in the superficial vein system were recorded, but did not prevent patients from receiving EVLT if the GSV was open and incompetent from the SFJ down to below the knee.

During EVLT itself, duplex scanning was particularly helpful in identifying the GSV at the puncture site, when necessary after full length down-scanning of the GSV from

the groin or up from the ankle. Duplex scanning was further an important means of localizing the precise position of the laser tip close to the SFJ before administration of tumescent local anesthesia, because afterward, because of the massive subcutaneous fluids, recognition of anatomical structures was almost impossible.

With scheduled duplex ultrasound scanning control examinations on days 1, 7, and 28, a full-length scanning of the treated vein was included as a means of demonstrating homogeneous thrombotic occlusion. Occlusive thrombosis was supposed when the vein was completely filled by an incompressible hypoechogenic mass and when no fluxes were detected within the vessel lumen. Similarly, in the region of the SFJ, the proximal ending of the thrombus was determined by means of compression and detection of fluxes. The distance of the proximal thrombus ending toward the junction with the deep femoral vein was measured. At day 28, the hypoechogenicity of the thrombus had almost disappeared. However, the lack of fluxes and the remaining incompressible vessel still allowed sufficient conclusions. Additional scanning of the deep vein system excluded a thrombotic affection there.

Testing for D-dimers in peripheral blood. After detection of EVLT-induced thrombotic occlusion, rather than an immediate closure of the GSV, we scheduled D-dimer testing for every patient. With the exception of the first six patients, D-dimer values (Tinaquant D-dimer, Roche Diagnostics, Mannheim, Germany) were scheduled to be determined from blood samples obtained 30 minutes and 1 day after the EVLT procedure. According to the manufacturer's data sheet, D-dimer values below 0.50 mg/L were considered to be within normal limits. However, because of technical reasons, blood sampling failed in four patients 30 minutes after EVLT.

Histopathologic examination. One patient gave informed consent to undergo EVLT as part of his routine varicose vein surgery procedure, which included extended high ligation of the SFJ and subsequent stripping of the incompetent parts of the GSV. EVLT was administered immediately after completion of extended high ligation, but before stripping of the GSV. The treated vein was left in place for another 15 minutes and then removed by means of stripping. The removed vein was photodocumented (Fig 1, *A*) and histopathologically examined with hematoxylin and eosin staining.

Mechanism of laser action. As a means of evaluating the mechanism of action of the 940-nm laser beam within the vein, an experimental set-up was designed (Fig 3, *A*). A silicone tube with an inner diameter of 6 mm was connected to a transparent tube with an inner diameter of 2 mm. The tube system was then filled with heparinized blood. From the opposite side, the laser fiber was inserted into the middle of the silicone tube. Different amounts of laser energy were then applied by means of variation of either laser power or pulse duration. With each laser pulse, the extension of the volume within the system was assessed by documenting the change in the blood level within the 2-mm tube. A cylindrical volume calculates as $V = h \times \pi r^2$ (eg, if a laser pulse produces a movement of the blood level of $h = 54$ mm, the laser generated steam volume calculates as $V = 54\ \text{mm} \times \pi[1\ \text{mm}]^2 = 170\ \text{mm}^3$, corresponding to a steam bubble length of 6 mm in a tube with a diameter of 6 mm). The temperature of the steam bubble is supposed to be close to 100° C and, once generated, should stay on this level constantly throughout its increase of volume, as it is known in the physics of phase transitions.

RESULTS

Twenty-six patients, 21 with unilateral and 5 with bilateral incompetent GSV, received EVLT by means of a 940-nm diode laser with tumescent local anesthesia. Nineteen patients were women (73%), and seven patients were men (27%), with 22 and 9 limbs treated, respectively. The median age of the patients was 57 years (range, 27-83 years). Before treatment, the median diameter of the GSV was 6.0 mm (range, 4.0-9.9 mm) at the level of the SFJ. In our relatively small cohort with a spectrum of clinical stages (Table I), the GSV diameter did not correlate with the body mass index of the patient (data not shown), the median of which was 26.6 (range, 20.0-39.7). The median amount of infiltrated tumescent local anesthesia was 650 mL per limb (range, 250-1000 mL).

Technical skills. Initially, before the use of duplex scanning for guided puncture of the GSV, access to the GSV failed in two of seven patients. These two patients underwent subsequent classic surgery. In four additional cases, insertion of the guidewire from below the knee to the SFJ was not possible in one step because of pronounced tortuosity of the GSV. In three of these four cases, an additional puncture of the GSV approximately 15 cm above the knee allowed treatment in two parts. In one case, EVLT was limited to the proximal 20 cm of the GSV because of the technical inability to obtain access to the more distal part of the GSV.

However, in all cases, duplex scanning-controlled placement of the fiber tip was achieved within a distance of 1 to 2 cm distal from the SFJ. In patients who were not overtly obese, this position could be visualized by means of transcutaneous illumination of the pilot laser beam. In our series of 31 limbs in 26 patients, this was true in four limbs of three male patients with a body mass index between 31.5 and 39.7. However, even in those obese patients, transcutaneous detection of the laser pilot beam was possible after applying gentle pressure to the overlaying skin.

Effects of endovenous laser treatment. During step-wise removal of the laser fiber, a median of 80 pulses (range, 22-116) of 15 J energy each were delivered, corresponding to a distance of 5 to 7 mm between laser pulses.

On days 1, 7, and 28 after treatment, thrombotic occlusion of the GSV was noted in all cases. In 30 of 31 limbs (97%), the thrombotic occlusion was complete from the distal puncture site, reaching proximally up to a median distance of 1.1 cm (range, 0.2-5.9 cm) from the SFJ. In one limb, the proximal occlusion of the GSV failed over a length of 20 cm despite complete occlusion of more distal parts of the GSV. The diameter of the GSV at the SFJ was 9.9 mm

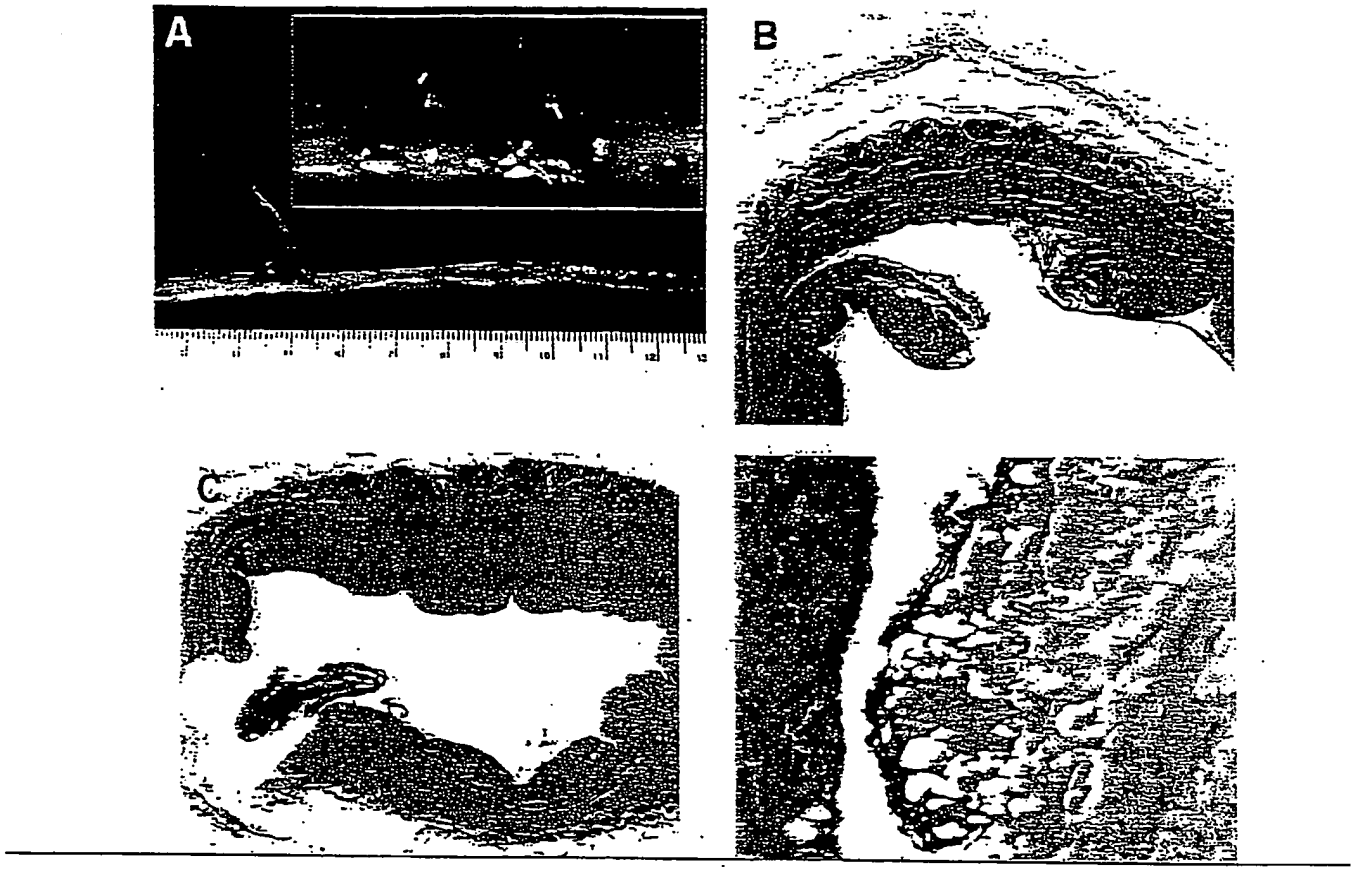


Fig 1. Macroscopic and microscopic hematoxylin and eosin-stained histopathologic examination of a GSV that has undergone EVLT before stripping. A, Outer surface of the endovenously laser-treated GSV. Dark spots resembling carbonization, or even full perforation of the vein wall, were caused by direct impact of the 940-nm laser beam. B, Intimal tear next to a non-perforating laser hit. C, Vein wall disruption caused by direct laser impact. D, High magnification of the margin area of vein wall disruption showing pronounced thermal damage, including carbonization.

and, therefore, the largest diameter of the whole series. Additionally, in this patient, we found by means of duplex scanning control a large caliber tributary with high blood flow feeding the GSV at the distal open point.

Adverse effects. After the local anesthetic effect subsided after EVLT, slight to moderate local pain was reported by all patients over the treated vein. Also, moderate ecchymoses, most likely caused by laser-induced perforation of the vein wall, could be observed in every patient at the inner thigh and knee region from the next day to approximately 2 weeks later. However, these ecchymoses were not as pronounced as they are usually with classic varicose vein surgery, and no hematoma was found. For the first 2 to 3 weeks after EVLT, also a slightly shorter period than frequently observed with classic surgical procedures, an induration was palpable along the treated GSV, and this was experienced by the patients as slight to moderate pain during extended movement of the leg. A thrombophlebitic reaction developed within an untreated varicose tributary at the distal thigh in two patients 2 and 5 days after EVLT. Oral treatment with diclofenac (75 mg, slow release, three times a day) resulted in immediate pain control. Hyperpigmentation developed in one patient over the thrombotically occluded GSV, which was still visible at 4 weeks after EVLT. All other patients were free of adverse effects at 4 weeks after the procedure. No other adverse effects or complications were reported.

D-dimers in peripheral blood. In 16 patients, D-dimer levels in peripheral blood were evaluated immediately after EVLT, and in 20 patients, blood samples were drawn on day 1 after EVLT (Table II). D-dimer levels were tested with normal results in all samples except one obtained 30 minutes after EVLT, with a median value of 0.39 mg/L (range, 0.09-0.80 mg/L). When D-dimer levels were tested at day 1 after EVLT in 20 patients, a median of 0.43 mg/L (range, 0.24-1.73 mg/L) was found. However, only seven blood samples showed D-dimer levels exceeding the upper limit of 0.50 mg/L. Although the

Table II. D-dimer levels in peripheral blood of patients who underwent endovenous laser treatment

	30 minutes after EVLT	1 day after EVLT	Ratio 1 day/30 min
Patients with1 limb treated	Median 0.30 mg/L (range 0.09-0.80) n = 13	Median 0.33 mg/L (range 0.24-1.73) n = 16	Median 1.39 (range 0.88-3.67) n = 13
Patients with 2 limbs treated	Median 0.45 mg/L (range 0.44-0.48) n = 3	Median 0.68 mg/L (range 0.50-0.91) n = 4	Median 1.82 (range 1.15-2.02) n = 3
All patients	Median 0.39 mg/L (range 0.09-0.80) n = 16	Median 0.43 mg/L (range 0.24-1.73) n = 20	Median 1.43 (range 0.88-3.67) n = 16

EVLT, Endovenous laser treatment.

absolute values remained mostly within normal limits, D-dimer levels were shown by means of intraindividual evaluation to increase from day 0 to day 1 in 15 of 16 patients who underwent both tests. The median increase ratio was 1.43 (range, 0.88-3.67), reflecting the process of thrombotic occlusion of the GSV. When separating the patients who received unilateral EVLT from patients who had a bilateral procedure (Table II), it looks as if patients with both limbs treated did not present the very low D-dimer values that are occasionally observed in patients with one limb treated. This observation might relate to two thrombotic processes instead of one, but also might be influenced by the thrombotic process having proceeded somewhat more in the first limb of those patients with bilateral EVLT. Unfortunately, the numbers are small in Table II and therefore do not warrant statistical analysis.

Pathologic examination of the endovenous laser treatment stripped vein. Macroscopically, the vein wall showed reddening, carbonization, or even perforation at those sites where the fiber tip was closest to the vein wall during delivery of laser energy (Fig 1, *A*). Either gross vein wall destruction associated with direct impact of the laser beam (Fig 1, *B-D*) or less pronounced heat-mediated vein wall injury (Fig 2, *B, C*) was demonstrated by means of microscopical examination of corresponding hematoxylin and eosin-stained slides. The heat injury demonstrated in Fig 2, *B* and *C*, was consistently detectable along the distance of 5 to 7 mm of vein wall, between the direct impact of two laser impulses, and is, in our opinion, the basis of a subsequent homogeneous thrombotic occlusion of the vessel. At those sites of direct laser action, the most destructive patterns of tissue damage can be observed: perforating and non-perforating vaporization of the vein wall, carbonization of the adjacent tissue margins, and intimal tear in response to the explosion-like delivery of high energy densities, called photo-disruption. However, because a stripping was performed after EVLT, some of the destruction observed, like intimal tears, may originate from the stripping procedure itself.

Mechanism of action of the 940-nm diode laser. Administration of different amounts of laser energy in the in vitro set-up was used as a means of evaluating the putative mechanism of laser action within the vein (Fig 3). During the experiments with heparinized blood in a silicone tube, we observed that a steam bubble formed during delivery of laser energy, and it collapsed immediately after discontinuation of the laser pulse. When we plotted the maximum volume of the laser-generated steam bubble against the amount of laser energy delivered, it showed a linear correlation (Fig 3, *C*). As calculated in the Methods section, a typical laser pulse with an energy of 15 J produced a steam-bubble of approximately 6 mm in a 6-mm diameter vessel. As shown in Fig 3, *C*, the formation of a steam bubble required a threshold energy of about 1.5 J. This threshold energy is needed to heat up the surrounding blood until it reaches boiling temperature. A laser pulse energy below this level would only heat the blood, without any steam bubble formation.

DISCUSSION

The principal finding in this study is that EVLT with a 940-nm diode laser system, when performed under tumescent local anesthesia, is a clinically feasible and well-tolerated technique. Because of vein access via an 18-gauge needle, it is a truly minimal invasive procedure, leaving a virtually invisible scar on the patient's skin.

The efficacy of EVLT in obtaining early occlusion of the GSV is very satisfactory. Even if these are very early results, immediate closure rates of 97% in our series and 100% reported by another group with the 810-nm diode laser[8] provide a rationale for further evaluating this new method.

A major emphasis of this study was placed on the mode of action of this novel technique: technically, the depth of penetration of a 940-nm laser beam into blood is only approximately 0.3 mm.[11] Also, the laser beam remains focused to a very small spot after leaving the fiber tip. Although these characteristics of the laser beam could explain a focal perforation of the vein wall (Fig 1, *C, D*) immediately adjacent to the fiber tip, this would not adequately explain the widespread injury to the vein wall observed in the vicinity of the perforation sites (Fig 2, *B, C*). With our in vitro set-up, we could identify steam bubble formation at the laser tip (Fig 3, *B*). The volume of the laser-generated steam bubble correlated directly to the laser energy (Fig 3, *C*). Because such a

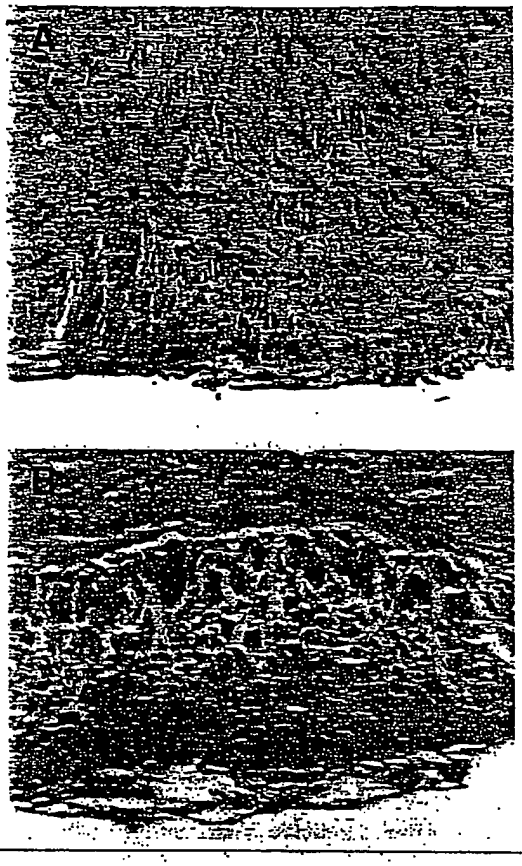


Fig 2. Indirect, steam bubble-mediated thermal damage after EVLT, several millimeters away from areas of direct laser impact. A, Control: normal varicose vein after stripping without earlier EVLT, with intact endothelium and distinct cellular contours. The nuclei are round to oval. B, EVLT resulted in a lift-off of endothelial cells, a denudation of the intima, loss of cellular contours, and fibrin deposition. Additionally, some areas show marked vacuolization of cells or even spongiosis. C, Swelling and waxy homogenization of collagen: Focal coagulation necrosis within the intima.

steam bubble formation is expected to occur within the vein lumen during EVLT, we propose that this phenomenon accounts for the thermal injury to an extended surface of the inner vein wall.

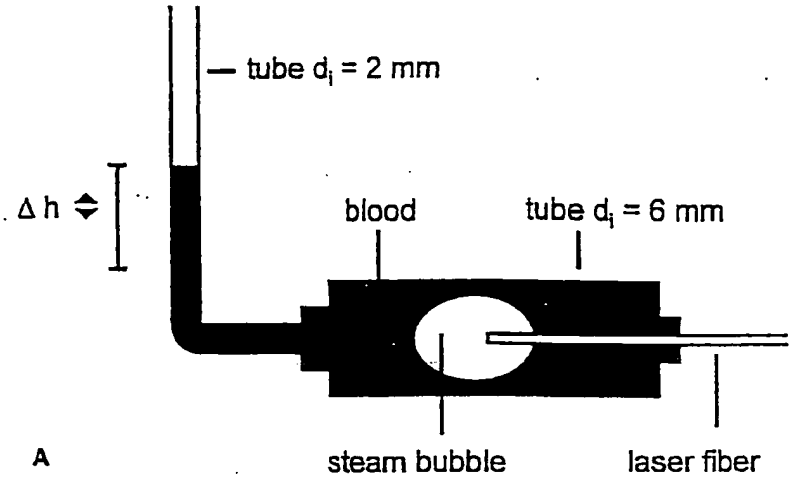
In a recent paper, Sadick et al[10] reported histopathological alterations of reticular veins and venulectasias after transcutaneous neodymium/yttrium-aluminum-garnet laser treatment that compare well with our findings. This opens the question of whether also in transcutaneous laser treatment of smaller veins the crucial damage of the vein may involve a similar steam bubble-mediated, hence indirect, thermal injury, rather than the immediate highly focused damage by the laser beam itself.

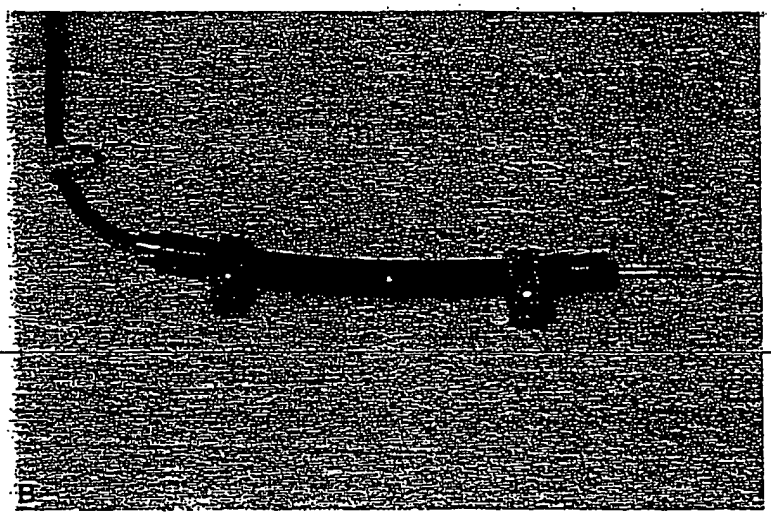
Steam bubble formation is a local, instantaneously reversible phenomenon that, after collapse of the bubble, poses no risk, such as gas embolism, to the patient. However, the extensive heat damage of the endothelium and the intima does induce the desired effect: full-length thrombotic occlusion of the vein. The complete thrombotic occlusion, however, is not detectable immediately after EVLT, but can be recognized at day 1 by means of a simple duplex scanning examination, which shows an incompressible, hypoechogenic cord in the lumen of the saphenous vein. This thrombotic occlusion is also reflected in all patients with an increase of D-dimer levels in peripheral blood by a median factor of 1.43. Because in our study and another study[5] no EVLT-induced deep vein thrombosis occurred, it seems very unlikely that the EVLT-induced thrombotic process of the GSV has a concomitant risk for deep vein thrombosis, as is known for superficial thrombophlebitis.[12] However, it remains unclear whether such an hypothetical risk of deep vein thrombosis does indeed exist or whether it is only so much lower compared with superficial thrombophlebitis[12] that it can only be detected in a larger series of patients.

Other commonly observed adverse effects with EVLT are induration along the GSV and mild-to-moderate ecchymoses. These ecchymoses, present for approximately 2 weeks, could be a cosmetic problem for patients who are expecting a minimally invasive, barely invisible treatment of their GSV incompetence. In this respect, EVLT would compare unfavorably with endoluminal radio-frequency closure. However, when weighed against the potential nerve damage after endoluminal radio-frequency treatment with subsequent skin paresthesis in as many as 16% of patients,[7] such an entirely reversible adverse effect seems quite acceptable.

Less frequent adverse effects, like thrombophlebitis of untreated tributaries or appearance of hyperpigmentation along the GSV, need to be followed and documented as the number of patients and EVLT procedures increase. At least the risk of thrombophlebitis could be avoided completely if varicose tributaries, unlike in the present series, are treated in the same session (eg, with mini-phlebectomy).[1,2]

Finally, it remains to be established whether EVLT induces effective long-term occlusion of the treated veins. Recurrent reflux, either originating from the SFJ or neoc-





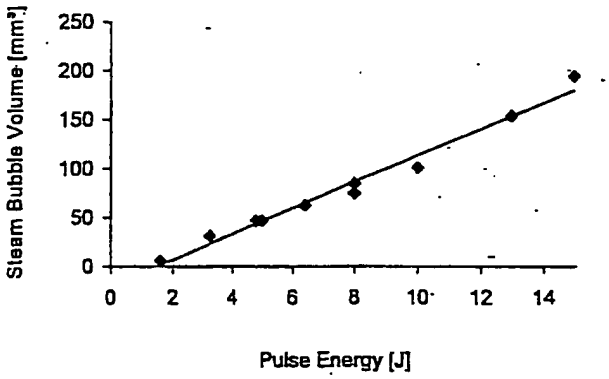


Fig 3. A, Schematic drawing of the in-vitro set-up for examining the laser-generated steam bubble formation. The laser fiber was inserted into a silicone tube of 6-mm-diameter filled with heparinized blood. During delivery of laser energy, heating and boiling of the blood finally lead to the formation of a steam bubble, pushing the corresponding blood volume out of the tube. Thus, the movement of the blood level in the smaller 2-mm-diameter tube allowed the calculation of the volume of the steam bubble in reverse. B, Visible steam bubble formation during delivery of a laser pulse of 15 J. C, Dependency of the steam bubble volume for various amounts of energy delivered by the laser beam.

curring within recanalized parts of the GSV, has to be followed closely. Only long-term follow-up in prospective trials will be able to answer this question.

We thank Mrs Weingärtner for skilled technical support and Mrs Gärtner for excellent preparation of the samples for histopathological examination.

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APPENDIX 3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/699,212	Confirmation No.: 2780
Applicant	:	David R. Hennings et al.	
Filing Date	:	October 30, 2003	
Title	:	Endovenous Closure of Varicose Veins with Mid Infrared Laser	
Group Art Unit	:	3739	
Examiner	:	David M. Shay	
Docket No.	:	15487.4002	
Customer No.	:	34313	

Mail Stop AMENDMENT
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DAVID R. HENNINGS

I, David R. Hennings, do declare and say as follows:

1. I am one of the inventors named in the above-identified application.

2. Attached hereto as Exhibits A-E are, respectively, true copies of product literature published by Dornier MedTech, biolitec, AngioDynamics, Vascular Solutions and Diomed, respectively.

Further, Declarant sayeth not:

CERTIFICATE OF MAILING (37 CFR §1.8)

I hereby certify, pursuant to 37 CFR §1.8, that I have reasonable basis to expect that that this paper or fee (along with any referred to as being attached or enclosed) would be mailed or transmitted on or before the date indicated with the United States Postal Service with sufficient postage as first class mail on the date shown below in an envelope addressed to Mail Stop Amendment, Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450.

Dated: July 5, 2005

Lynne Fulmer

Applicant	:	David R. Hennings et al.
Appl. No.	:	10/699,212
Examiner	:	David M. Shay
Docket No.	:	15487.4002 (Formerly NSL-501)

I declare under penalty of perjury that the foregoing is true and correct. Executed this 30 day of June, 2005 at Roseville, California.

David R. Hennings

IDS REFERENCES

☐ FOR

VenaCure Precision 980™ Laser Specifications

Laser Type	Integrated GaAlAs semiconductor laser arrays
Wavelength	980 nm
Output Power	15 W
Power Range	1-15 W
Increments	1 or 5 W
Operating Modes	Continuous, Pulsed
Pulse Duration ON/OFF	0.01 to 99.9 sec
Aiming Beam	635 nm; 4 mW
Cooling	Air cooled
Weight	15 lbs (6.8 kg)
Dimensions	14" x 9" x 7"
Power Requirements	110/220 V
Fiber Connector	Standard SMA 905

Ordering Information

NEW VenaCure™ Procedure Kit 45cm	11402001
NEW VenaCure™ Procedure Kit 65cm	11402002
Precision 980™ Laser	11400201
Laser Safety Glasses	11401601
Physician Welcome Kit	11402301
Patient Brochure Holder	11402601
Patient Brochures	11402701
Patient Education Video	11402501
Patient Direct Mailer Card	11402801

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INCORPORATED

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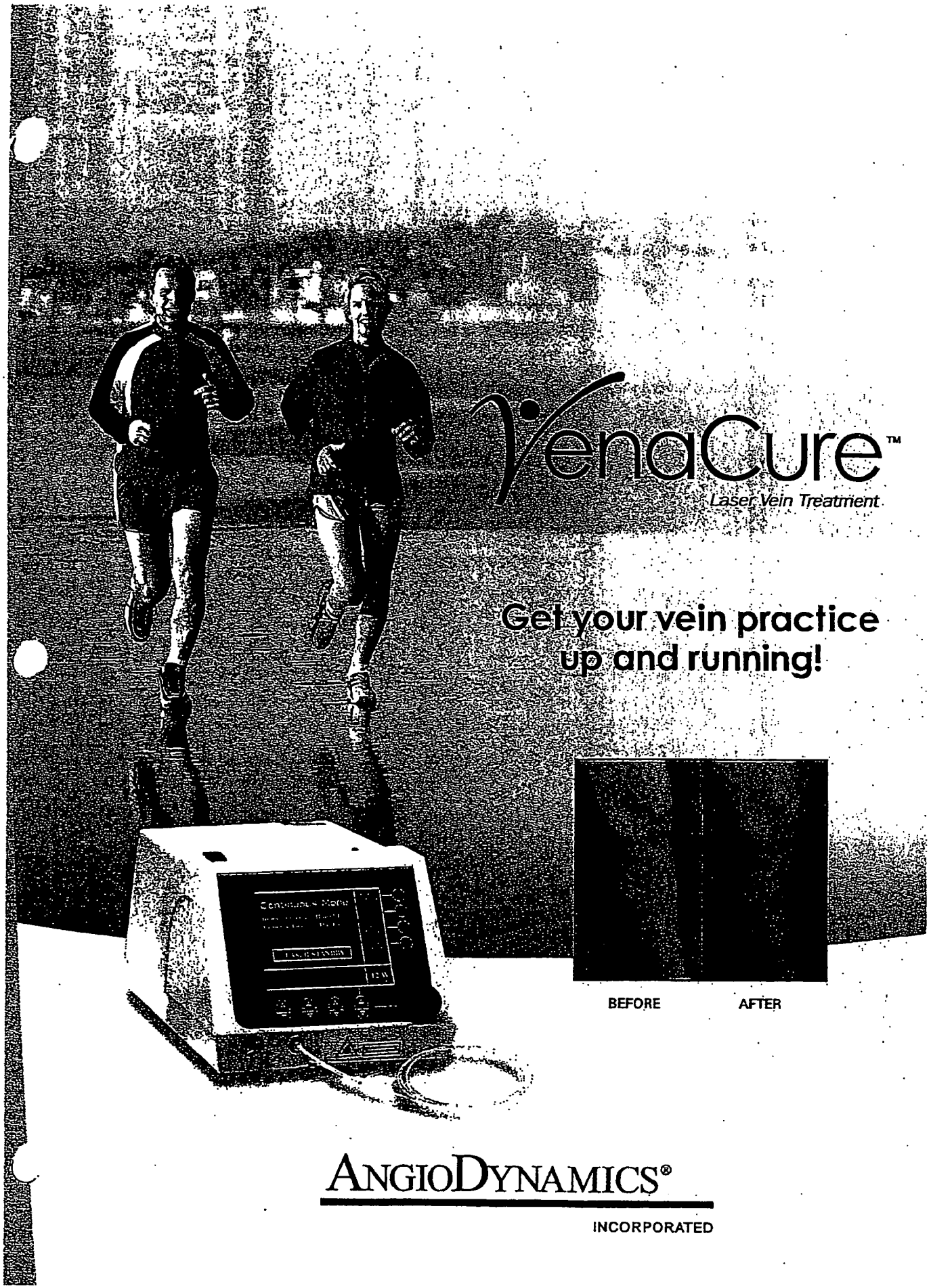
Phone: 518-798-1215 Fax: 518-798-1360 Toll-Free U.S.A.: 1-800-772-6446
www.angiodynamics.com



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Laser Vein Treatment

Get your vein practice up and running!

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INCORPORATED

IDS REFERENCES

☐ FOR

VariLase® VALUE

Vascular Solutions' commitment to helping you build a successful vein practice

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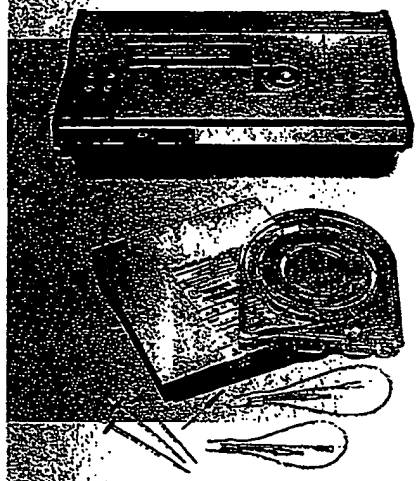
Professional Service

Professional Support

Vascular SOLUTIONS

Vari-Lase Value... all the professional products, services and support you need to build a successful vein practice



A complete line of professional Vari-Lase products for endovenous laser therapy

- Vari-Lase procedure kits
- Vari-Lase 810 Laser Console
- Fibers, catheters and other product accessories

Vari-Lase products are designed with the vein practice in mind. The Vari-Lase kit is not just a box of components but a professionally designed procedure kit for endovenous laser treatment of superficial venous reflux. This kit comes in a variety of configurations. In addition, Vascular Solutions offers a full line of micro-introducer kits, tear-away kits and guidewires – everything you need to keep your practice running smoothly.

Physician Training - Clinical & Business

Vascular Solutions is dedicated to providing the finest vein care training available for physicians and their staff.

With training centers located throughout the United States and Germany, Vascular Solutions offers its partners the most comprehensive education available on the clinical procedures and practice management of total vein care.

Marketing & Advertising Support

Vascular Solutions provides real assistance in getting the word out about your vein practice. Marketing assistance includes:

- Selection of customized display ads designed for use in newspapers, yellow pages and various graphic designs
- Set of customizable press releases for use in a wide range of publications
- Consultation with a designer when preparing advertisements
- Powerpoint presentation on vein disease for use in public forums, such as health fairs

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Vari-Lase Endovenous Procedure Kit.

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Vari-Lase endovenous procedure kit »

Vari-Lase- the professional endovenous laser procedure kit.

Better. Easier. Professional.

Vari-Lase is not just a box of components but a professionally designed procedure kit for endovenous laser treatment of superficial venous reflux.

The Vari-Lase procedure kit is indicated for the treatment of varicose veins associated with superficial reflux of the great saphenous vein.
The Vari-Lase procedure kit can be used in conjunction with any solid state diode laser console accepting a standard SMA-905 connector and operating at a wavelength of 810nm, 940nm, or 980nm and a maximum power of 15W.

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Vascular Solut
6464 Sycar
Minneapolis,
763

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IDS REFERENCES

☐ FOR

EVLT® non-surgical endovenous laser treatment

The Greatest Experience in Eliminating Varicose Veins™

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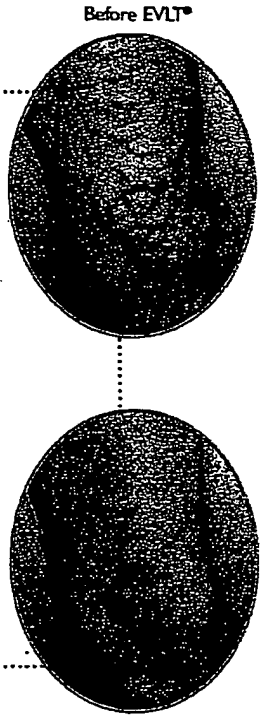
Advanced Technology

Expert Training

Practice Growth



Equipment

EVLT® is performed with a 15 watt, 810nm DIOMED Diode Laser that is:

Compact and portable – fits in the treatment room and can be transported easily

Quick to set up – runs from a standard electrical wall socket; ready for use in seconds

Easily maintained – designed as a solid state system and has no moving parts

Easy-to-use – gives immediate access to treatment options and operating modes

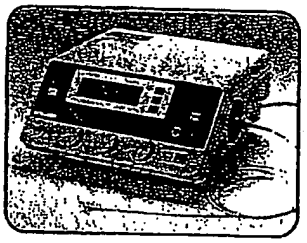
Versatile – can be used in transdermal applications to treat spider veins and smaller vascular lesions (D30 Plus)

Disposable accessories are provided in a convenient "single use" EVLT® Procedure Kit that includes:

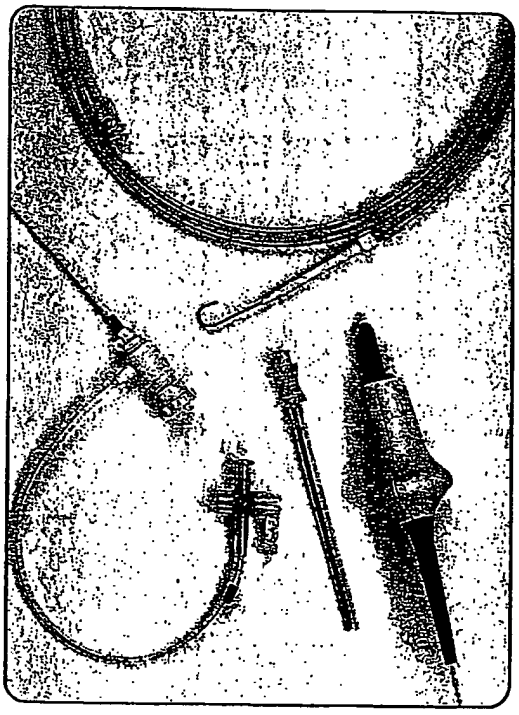
- EVLT® laser fiber with SiteMarks™
- Percutaneous entry needle or micro-access kit
- Guide wire
- Custom introducer sheath with graduated markings (standard and long version)

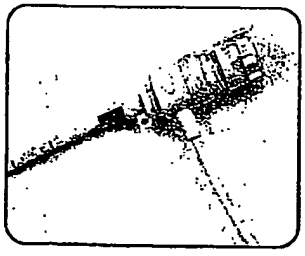
PRECISELY THE RIGHT WAVELENGTH

The specific 810nm wavelength used in EVLT® is set to target vein treatment. Its safety and efficacy have been tested and proven in multiple clinical studies.



A red aiming beam identifies the exact position of the fiber within the vein.





Specialists in Interventional Radiology, Phlebology, and Vascular Surgery helped design the EVLT® procedure kit with their patients and practices in mind. It is easy to use, economical, and convenient.

Safety Ensured: The first SiteMark™ tells the user that the fiber tip is at the end of the sheath. Drawing the sheath back to the second SiteMark™ brings the fiber out three centimeters and positions it properly at the saphenofemoral junction.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/699,212	Confirmation No.: 2780
Applicant	:	David R. Hennings	
Filing Date	:	October 30, 2003	
Title	:	Endovenous Closure of Varicose Veins with Mid-Infrared Laser	
Group Art Unit	:	3735	
Examiner	:	David M. Shay	
Docket No.	:	15487.4002	
Customer No.	:	34313	

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P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL APPEAL BRIEF AND REQUEST FOR ORAL HEARING

Sir:

Real Party in Interest

CoolTouch, Inc., a wholly-owned subsidiary of New Star Laser Company, is the real party in interest.

Related Appeals and Interferences

None.

CERTIFICATE OF MAILING, 37 CFR §1.8

I hereby certify, pursuant to 37 CFR §1.8, that I have reasonable basis to expect that that this paper or fee (along with any referred to as being attached or enclosed) would be mailed or transmitted on or before the date indicated with the United States Postal Service with sufficient postage as first class mail on the date shown below in an envelope addressed to the Commissioner for Patents, Mail Stop Appeal Brief-Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Dated: September 11, 2009

Lynne Fulmer

Status of Claims

Claims 1-17 and 19-23 and 25-46 are pending in this application. These claims have all been rejected and are the claims on appeal. Claims 18 and 24 have been cancelled.

Status of Amendments

All amendments which Applicant has filed have been entered.

Summary of Claimed Subject Matter

There are four independent claims, which are claims 1, 14, 25 and 35, in the present application. Claims 1, 25 and 35 are method claims and claim 14 is a system claim, all of which are directed to the treatment varicose veins.

Claim 1 reads as follows:

> "1. An endovenous method of treating a varicose vein comprising the step of using a laser having a wavelength between about 1.2 and about 1.8 um to heat and shrink collagen in a varicosed vein to destroy the functionality of the varicose vein."

This method is illustrated schematically in Figures 3A-6 and in more detail in Figures 7 and 8. As described in paragraphs 47-50 of the application, the method comprises using a laser fiber 306 (which has been deployed through dilator 300) into vein 202. This is described in paragraph 47 of the specification as follows:

> "FIG. 3B is a representative view showing the use of the introducer or dilator 300 with the laser fiber 306 passing through the lumen 302 of the dilator 300 and into the GSV (greater saphenous vein) 202 ..."

The use of a laser having a wavelength between about 1.2 and about 1.8 um is described in paragraph 52 as follows:

> "The 1.2 to 1.8 um laser wavelengths are ideally suited to penetrate the small amount of remaining blood in the vessel 200 but also is much more strongly absorbed in the vessel wall 704 by collagen. Most of the energy is concentrated in the wall 704 for heating and shrinkage and is not transmitted through to surrounding tissue 702."

Claims 2-13, 26, 29, 32, 37 and 41 are dependent, directly or indirectly on claim 1. Claims 2, 3, 6, 26, 29, 32, 37 and 41 are directly dependent upon claim 1. Claims 4 and 5 are dependent upon claim 3. Claims 7-9 and 12 are dependent upon claim 2. Claims 10-13 are dependent upon claim 9. Claim 2 recites the use of a fiber optic which is disclosed at page 13, line 19 and illustrated in Figure 1 as element 106. Claims 3-5 are directed to the use of a pullback device which is disclosed at page 13, line 19 and original claim 3 and illustrated in Figure 1 as element 104. Claim 6 recites the preliminary step of removing blood from a vein prior to treatment with laser energy, page 15, lines 17 and 18. Claim 7 recites the use of an introducer catheter to introduce the fiber optic into the vein which is disclosed at page 14, lines 3-5 and illustrated in Figure 3B in which the introducer is shown as element 300. Claim 8 is directed to the use of a diffusing tip fiber optic which is disclosed at page 18, line 4 through page 20, line 2 and illustrated in Figures 9A, 9B and 9C. Claims 10-13 are directed to the use of a thermal sensor which is described at page 16, line 13 through page 18, line 2 and illustrated in Figure 6 in which the thermal sensor is shown as element 600. Claim 26 recites that the laser energy has a wavelength of about 1.32 um which is disclosed at page 12, line 23, page 16, line 2, 20, line 16, page 20, line 24, page 22, line 5 and page 23, line 22, for example. The use of a Nd:YAG laser is disclosed, for example, at page 16, line 1, page 24, line 2 and at page 22, line 25. Claim 32 recites that the laser energy preferentially heats the water in the wall of the vein which is disclosed at page 9 line, 10 and at page 23, lines 22 and 23, for example. Claim 41 is directed to

heating the target chromophore to a temperature not greater than 85° C which is disclosed at page 8, line 14.

Claim 14 reads as follows:

> "14. A system for endovenous treatment of varicose veins comprising the following:
> A laser having a wavelength between about 1.2 and about 1.8 um; and
> A fiber optic laser delivery device having a proximal end and a distal end, for delivery of laser energy from the distal end of the fiber optic laser delivery device to the inside wall of a varicose vein wherein the functionality of the varicose vein is destroyed and collagen in the varicosed vessel wall can be heated and shrunk."

The system of claim 14 is illustrated in Figure 1 and in more detail in Figure 3B. In Figure 1, laser console 102 is illustrated and it is disclosed in paragraph 54 that laser 102 can be used to provide laser wavelengths in the 1.2 to 1.8 um region. In Figure 3B, the fiber optic laser device 306 is illustrated and described in paragraph 47 as follows:

> "FIG. 3B is a representative view showing the use of the introducer or dilator 300 with the laser fiber 306 passing through the lumen 302 of the dilator 300 and into the GSV (greater saphenous vein) 202 ..."

The function of this system to deliver energy to heat and shrink the collagen in the vessel wall is described as follows in paragraph 52:

> "The 1.2 to 1.8 um laser wavelengths are ideally suited to penetrate the small amount of remaining blood in the vessel 200 but also is much more strongly absorbed in the vessel wall 704 by collagen. Most of the energy is concentrated in the wall 704 for heating and shrinkage and is not transmitted through to surrounding tissue 702."

Claims 15-17, 19-23, 27, 30 and 33 are dependent, directly or indirectly, upon claim 14. Claims 15-17, 21, 27, 30 and 33 are directly dependent on claim 14. Claims 19 and 20 are

dependent on claim 17. Claim 22 is dependent on claim 21 and claim 23 is dependent on claim 23. Claim 15 recites a pullback device which is disclosed at page 13, line 19 and illustrated as element 104 in Figure 1. Claim 16 recites the administration of anesthesia to cause swelling and compression of the tissue surrounding the varicose vein which is disclosed at page 14, lines 15-18 and illustrated in Figure 7. Claim 17 recites an introducer catheter which is disclosed at page 14, lines 3-5 and illustrated in Figure 3B as element 300. Claims 19 and 20 recite a diffusing tip on the fiber optic which is disclosed at page 18, line 4 through page 20, line 2 and illustrated in Figures 9A, 9B and 9C. Claims 21-23 recite a thermal sensor and temperature controller which are disclosed at page 16, line 13 through page 18, line 2 and illustrated in Figure 6. Claim 27 recites a laser having a wavelength of 1.32 um which is disclosed, for example, at page 12, line 23, page 16, line 2, page 20, line 24, page 22, line 25, page 23, line 22 and page 24, line 2. Claim 30 recites a Nd:YAG laser which is disclosed at page 16, line 1, page 22, line 25 and page 24, line 2. Claim 33 recites that the system is adapted to preferentially heat water which is disclosed, for example, at page 23, lines 22 and 23 and illustrated in Figure 10.

Claim 25 reads as follows:

> "25. An endovenous method of treating varicose veins with laser energy to heat and shrink collagen in the vein and to destroy the functionality of the varicosed vein, the method comprising the following steps:
> inserting a laser delivery device into the varicose vein;
> delivery laser energy having a wavelength between about 1.2 and about 1.8 um to the varicose vein; and
> retracting the laser delivery device through the varicose vein, thereby heating and shrinking the collagen in the vein and destroying the functionality of the varicose vein."

The first two steps of claim 25 are illustrated and described as set forth above with regard to claim 1. The step of retracting the laser delivery device is described in paragraph 51 as follows:

> "The catheter 32 is connected to a motorized pullback device 104 either inside or outside of the sterile field 108 of the patient. The procedure begins by starting the pullback for about 2 or 3 mm and then turning the laser 102 on at about 5 watts of power. The pullback device is illustrated schematically in Figure 1 as element 104. "

Claims 28, 31 and 34 are each directly dependent on claim 25. Claim 28 recites that the laser has a wavelength of about 1.32 um as disclosed, for example, at page 23, line 22, page 12, line 33, page 16, line 2, page 22, line 5 and page 20, line 16. Claim 31 recites a Nd:YAG laser as disclosed at page 16, line 1. Claim 34 recites that the laser energy preferentially heats water as described at page 9, line 10 and at page 23, lines 22 and 23 and illustrated in Figure 10.

Claim 35 reads as follows:

> "35. A method of treating varicose veins, comprising
> providing a beam of light comprising a wavelength in the range of about 1200 nm to about 1800 nm; and
> delivering endovascularly the beam of light to target a chromophore comprising water in the wall of a targeted varicose vein to treat the vein."

This method is illustrated in Figure 3B and is described in paragraph 47 as follows:

> "FIG. 3B is a representative view showing the use of the introducer or dilator 300 with the laser fiber 306 passing through the lumen 302 of the dilator 300 and into the GSV (greater saphenous vein) 202..."

According to the preferred embodiment of the method and apparatus of the present invention. the method is further described in paragraph 52 which states:

> "The 1.2 to 1.8 um laser wavelengths are ideally suited to penetrate the small amount of remaining blood in the vessel 200 but also is

> much more strongly absorbed in the vessel wall 704 by collagen. Most of the energy is concentrated in the wall 704 for heating and shrinkage and is not transmitted through to surrounding tissue 702."

Water absorption of laser energy in the region between about 1200 nm to about 1800 nm is disclosed in paragraph 65 and is illustrated in Figure 10. In paragraph 65, it is stated:

> "It will further be observed that the region between about 1200 nm to about 1800 nm shows low hemoglobin and higher water absorption, which is a key to the present invention."

Claims 38-40 and 42-46 are dependent, directly or indirectly, on claim 35. Claims 38, 40, 44 and 45 depend directly on claim 35. Claims 39 and 42 depend on claim 38, claim 43 depends on claim 42 and claim 46 depends on 45. Claim 38 is directed to the use of a fiber optic which is disclosed at page 13, lines 19 and 20 and illustrated in Figure 1 wherein element 106 is the fiber optic. Claim 39 recites the use of a diffusing tip which is disclosed at page 18, line 3 through page 20, line 2 and illustrated in Figures 9A, 9B and 9C. Claim 40 recites that the treatment reduces the size of the varicose vein which is disclosed at page 20, lines 20-22. Claims 42 and 43 recite the use of a pullback device which is disclosed at page 13, lines 19 and 20, original claim 2 and illustrated in Figure 1 where the pullback machine is element 104. Claim 44 recites removing blood from the vein prior to treatment which is disclosed at page 14, line 20. Claim 45 recites the laser power of 1 to 20 watts which is disclosed at page 15, lines 12 and 13. Claim 46 recites a power of 5 watts which is disclosed at page 15, line 12.

With further regard to the dependent claims, the fiber optic delivery device of claims 2, 14 and 38 is illustrated as element 306 in Figure 3B and is described in paragraph 47.

The procedure of claim 5 in which the pullback device begins retraction of the fiber optic device prior to initiating delivery of the laser energy is disclosed in paragraph 51.

The use of a diffusing tip on the optical fiber recited in claims 8, 19 and 39 is illustrated in Figures 9A, 9B and 9C and is described in paragraphs 62, 63 and 64 as well as in paragraphs 59-61.

The non-contact thermal sensor of claims 9 and 21 is described in paragraphs 55 and 56. Providing the fiber optic laser delivery device with a thermal sensing element as recited in claim 12 is described in paragraph 55.

The procedure of modulating the laser power based on the sensed temperature as recited in claims 13 and 23 is described in paragraph 55.

The use of a laser having a wavelength of about 1.32 um as recited in claims 26-28 and 37 is disclosed in paragraph 53 and paragraph 79.

The use of a Nd:YAG laser as recited in claims 29-31 is disclosed in paragraphs 53 and 54.

The preferential heating of water in the wall of the vein as recited in claims 33-35 is disclosed in paragraphs 65 and 79. It is also disclosed in paragraph 21.

The use of laser power between about 1 to about 20 watts as recited in claim 45 and the use of laser power of about 5 watts as recited in claim 46 is described in paragraph 51.

There are four independent claims, which are claims 1, 14, 25 and 35. Claims 1, 25 and 35 are directed to a method of treating varicose veins and claim 14 is directed to a system for treating varicose veins. Method claims 1 and 25 and system claim 14 recite treatment using a laser having a wavelength between about 1.2 um (1200 nm) and about 1.8 um (1800 nm). Claim 35 recites a method using this range of wavelengths to target a chromophore comprising water in the wall of a targeted varicose vein.

The method of claims 1, 25 and 35 is illustrated schematically in Figures 3A-6. The method is illustrated in more detail in Figures 7 and 8. This method is described in paragraphs 47-50 of the application. The method comprises introducing a dilator 300 into the vein to be treated with the laser fiber 306 passing through a lumen 302 of the dilator 300 and into vein 202. Once the laser fiber is properly positioned, laser energy is passed therethrough at a wavelength of about 1.2 to about 1.8 um to preferentially heat the water in the wall of the vein rather than blood which maybe present in the vein.

The use of a pull back device 104 is disclosed in paragraph 51 of the application. The use of the diffusers 902, 920 and 926 illustrated in Figures 9A-C is disclosed in paragraph 62-64 of the application. The use of thermal detector 600 is illustrated in Figure 6 and is described in paragraphs 55-57 of the application.

The system of claim 14 comprising a laser 102 and a fiber optic delivery device 306 is illustrated in Figures 1 and 3A-8.

The preferential absorption of laser energy by the water in the wall of a targeted varicose vein recited in claim 35 is disclosed in paragraphs 21, 52, 65, 79, and FIG. 10 of the application. This localizes the heating caused by the laser energy in the vessel wall 704 thereby significantly inhibiting the heating of surrounding tissue 702 as described in paragraphs 22, 23, 52, and 79.

Grounds of Rejection To Be Reviewed on Appeal

Claims 1, 2, 6, 7, 25, 35-38, 40, 41 and 44-46 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Goldman Patent No. 6,258,084 in combination with Sinofsky Patent No. 5,196,004 and Dew Patent No. 4,854,320. Claims 3-5, 42 and 43 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Goldman in combination with Sinofsky, Dew and Roth

Patent No. 5,207,672. Claims 8 and 39 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Goldman in combination with Sinofsky, Dew and Conn PCT Application No. WO 92/17243. Claims 9-13 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Goldman, in combination with Sinofsky, Dew and Makower PCT Application No. WO 93/15664. Claims 14-17 and 20-23 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Makower, in combination with Roth and Dew. Claim 19 has been rejected as unpatentable over Makower, in combination with Dew, Roth and Conn.

Claims 1, 2, 6, 7, 25, 35-38, 40, 41 and 44-46 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Goldman Patent No. 6,258,084 in combination with Sinofsky Patent No. 5,196,004 and Dew Patent No. 4,854,320. Claims 3-5, 42 and 43 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Goldman in combination with Sinofsky, Dew and Roth Patent No. 5,207,672. Claims 8 and 39 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Goldman in combination with Sinofsky, Dew and Conn PCT Application No. WO 92/17243. Claims 9-13 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Goldman, in combination with Sinofsky, Dew and Makower PCT Application No. WO 93/15664. Claims 14-17 and 20-23 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Makower, in combination with Roth and Dew. Claim 19 has been rejected as unpatentable over Makower, in combination with Dew, Roth and Conn.

Evidence Appendix

Applicant has submitted declarations under 37 CFR 1.132 together with exhibits. These declarations and exhibits are attached hereto as an evidence appendix in conformance with 37 CFR

41.37(c)(1)(ix) as Appendix 2. This evidence was entered by the Examiner in the Office Action dated March 13, 2009.

Historical Note

This Appeal has something of an unusual history. This is not the first Appeal Brief to be filed in this application and the Office Action dated March 13, 2009, is not the first Final Rejection from which an Appeal has been taken. The earlier appeal never got past the Examiner's Answer stage because a new ground of rejection was raised in that Answer.

There was an earlier Final Rejection dated February 12, 2007 from which Applicant appealed and filed an Appeal Brief on October 29, 2007 (which was objected to on formal grounds and Applicant filed a corrected appeal brief on November 28, 2007). Almost one year later, the Examiner filed an Examiner's Answer on November 13, 2008 stating that it was in response to an appeal brief filed "November 28, 2008" (sic), (November 28, 2007 was the actual date). This Board noted that the Examiner's Answer made a new ground of rejection and Applicant was given the option of requesting that prosecution be re-opened under 37 CFR 1.111. Applicant did request re-opening of prosecution and, on January 13, 2009, responded to the new ground of rejection set forth in the Examiner's Answer. This response included a Declaration of David R. Hennings dated December 22, 2008 (which was the second Hennings Declaration to be filed in this application) and the Declaration of Mitchel P. Goldman dated December 23, 2008, together with Exhibit 1 to the Hennings Declaration and Exhibits 1-3 to the Goldman Declaration. The Examiner then rendered another Final Rejection dated March 13, 2009 and it is this Final Rejection to which the present Appeal is directed.

The issues presented in this Appeal involve both (a) the usual comparison of the claims with the prior art and (b) the Examiner's refusal to give effect to the evidence submitted in support of patentability. Thus, we will first discuss the prior art rejections and why we believe they are erroneous and then discuss the extensive evidence which conclusively refutes the Examiner's positions and what we believe to be the Examiner's improper refusal to give this evidence the weight to which it is entitled.

The Rejections Are In Error

Claims 1, 2, 6, 7, 25, 35-38, 40, 41 and 44-46 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Goldman '084 in combination with Sinofsky Patent No, 5,196,004 and Dew et al. Patent No. 4,854,320. Goldman is directed almost entirely to RF heating of varicose veins and contains only one throw-away sentence which mentions lasers at column 7, lines 53-59, and which says that "other forms of energy such as microwaves, ultrasound, direct current, unrelated heated fluid, radiant light, and lasers can be used....". This single mention of lasers in Goldman is non-enabling and occurs only in the context of a listing of several possible alternatives to the use o RF energy, none of which are otherwise mentioned or enabled.

The law relating to enablement, and the lack of it, makes it plain that making a passing reference to an alternate system does not constitute compliance with the enablement requirement of 35 USC 112. For example, in Sitrick v. Dreamworks, LLC, 516 F.3d 993 (Fed. Cir. 2008), the patent was directed to an intercept adapter interface system (IAIS) and a Controller 260C for integrating images into a predefined audio/visual presentation. The '825 patent-in-suit disclosed that "this invention relates to predefined video and audio/visual presentations such as **movies** and **video games**", but the remaining disclosure was directed in its entirety to video games and there was **no**

further disclosure relating to movies. At 516 F.3d 1000, the Court noted, "the specifications do not disclose how the IAIS or Controller 260C would function for movies" and went on to say that the "patents do not teach how to implement the internal 'intercept logic functioning' of Controller 260C in the context of movies." The Federal Circuit then held, 516 F.3d 1002-03 that "all asserted claims of the '825 patent are not enabled."

Similarly, in Auto. Techs. International v. BMW of N.Am., Inc., 501 F.3d 1274, 1285 (Fed. Cir. 2007), the Federal Circuit said:

> "Disclosure of only mechanical side impact sensors does not permit one skilled in the art to make and use the invention as broadly as it was claimed, which includes electronic side impact sensors."

The Federal Circuit's decision in Medtronic Navigation, Inc. v. Brainlab, 222 Fed. Appx. 952 (Fed. Cir. 2007), which was not selected for publication in the Federal Reporter and is not precedential, nevertheless serves as a useful guide to the state of the law on enablement. In Medtronic, the patent was directed to an acoustic or ultrasound range finding system and to an electromagnetic position and orientation system to track the movement of an object, but also contained the statement:

> "An optical system can be used as an alternative to the acoustic system described earlier."

There was no other disclosure relating to an optical system. The Federal Circuit held:

> "There is no enabling description of how to make and use an optical tracking system...."

Thus, although Medtronic is not precedential, it is consistent with Sitrick with regarding to finding a lack of enablement when a specification contains nothing more than a single disclosure of

an otherwise unmentioned alternative. So it is here. There is but a single word in Goldman relating to lasers without any further mention of such devices.

As stated in Fiers v. Revel, 984 F.2d 1164, 1171 (Fed. Cir. 1993) such a minimal, non-enabling disclosure is "an attempt to preempt the future before it has arrived."

Furthermore, we have the benefit of the acknowledgement of Goldman himself that the '084 patent does not enable lasers or laser treatment of varicose veins. Goldman's own Declaration dated December 23, 2008, in paragraph 5, states:

> "The work upon which my Patent No. 6,258,084 is based involved only the use of tumescent anesthesia in the RF treatment of varicose veins and no work of any sort was done involving the use of lasers. Prior to filing the application which became Patent No. 6,258,084, we had no experience or knowledge which would permit us to enable the use of lasers to treat varicose veins. For example, we did not know which laser wavelengths might be useful nor did we know what power levels might be safe and effective."

This is a direct and unequivocal statement by one of the inventors of the Goldman '084 patent (who is also one of the inventors named in the present application) that his '084 patent is not enabling with regard to lasers. As we will discuss in more detail below, the Examiner, at pages 6 and 7 of the Final Rejection, attempts to sidestep the Goldman Declaration by resorting to:

1. The totally irrelevant fact that claim 31 of the Goldman '084 patent does not recite tumescent anesthesia;

2. A refusal to recognize that the word "we" in the Goldman Declaration refers to Goldman and his co-workers; and

3. A seriously misguided attempt to find an inconsistency between the Goldman Declaration and the oath of inventorship in the '084 patent.

The Examiner's arguments are misplaced and unsupported. In brief:

1. The absence of a recitation of tumescent anesthesia in claim 31 of the '084 patent has absolutely nothing to do with whether lasers are enabled;

2. The word "we" in Goldman's Declaration plainly refers to Goldman and his co-workers on the subject matter of the '084 patent; and

3. The Examiner has built a house-of-cards argument based on the inventors oath in the '084 patent because **none of the original claims recited a laser!**[1] Thus, there is absolutely no inconsistency between the inventors' oath in the '084 patent and the Goldman Declaration. Furthermore, even if the original claims did recite a laser, no court has ever mentioned an inventor's oath as having any consequence when making a determination regarding enablement.

Thus, the Examiner's conclusion as stated at page 7 of the Final Rejection as follows:

> "Thus, weighing Declarant's statement, wherein Declarant holds a vested interest in the issuance of the instant application, against the evidence afforded by a signed declaration in a U.S. patent (which includes a presumption of operability), the examiner is not persuaded by Declarant's current stance, that the subject matter of the claims of the Goldman et al. ('084) is inoperable."

is devoid of any support in the record. Furthermore, the issue is **not** the **operability** of the **claims** of the Goldman '084 patent, but rather the lack of **enablement** of lasers in the **specification** of that patent.

[1] Applicants ask that this Board take judicial notice of the original claims of the application which became the '084 patent. For the convenience of the Board, these claims are provided in the appendix to this brief.

The '084 patent discloses nothing with regard to laser wavelengths or power levels. The choice of laser wavelengths is of crucial importance. Unlike conductive and connective heating, laser heating is highly selective and the laser will only heat materials which are a chromophore for a given wavelength, but not other materials which are not chromophores for that wavelength. The claims in the present application recite a wavelength of about 1200-1800 nm which was a departure from the prior laser treatment of varicose veins (which the Examiner has refused to regard as meaningful) such as Navarro Patent No. 6,398,777 which discloses the use of lasers having wavelengths of 500-1100 nm.

Thus, merely mentioning lasers generally, as Goldman '084 does, leaves the reader entirely in the dark as to what lasers, with what wavelengths, for what chromophores might be tried in an effort to treat varicose veins. This is the very definition of undue experimentation. In addition, the type of laser, power levels and duration of treatment must also be determined requiring even more experimentation. Some of the factors to consider in the experimentation required to determine the type of laser, the laser wavelength, the power levels and dose duration for a given use are outlined in Sinofsky Patent No. 5,196,004, in cols. 2-5.

This lack of disclosure in Goldman is also in contrast to the disclosure in Navarro Patent No. 6,398,777,[2] which is regarded by those in the art as representing the first use of lasers to treat varicose veins, which, at col. 5, lines 17-23, at col. 6, lines 13-18 and at col. 5, lines 45-49, discloses wavelengths of 50-1100 nm, power levels of 5 to 20 watts and treatment duration of 0.2-10 seconds.

[2] The Examiner has steadfastly and mysteriously refused to rely on the Navarro patent as a reference, *see* p. 3, lines 2-13, of the Final Rejection.

Thus, Navarro provides the type of disclosure which is entirely lacking in Goldman's '084 single nonenabling mention of lasers.

Since Goldman '084 is nonenabling, the attempt to combine Sinofsky and Dew et al. with Goldman is an exercise in futility and the rejection of claims 1, 2, 6, 7, 25-38, 40, 41 and 44-46 over this combination of references cannot stand.

Furthermore, even if Goldman '084 were enabling, this rejection would be in error because the secondary references do not remedy the deficiencies of Goldman and are completely unrelated to Goldman and to each other and cannot be properly combined. Goldman '084 relates to treatment of varicose veins, Sinofsky is directed to removal of atherosclerotic plaque and Dew et al. is concerned with wound healing. Goldman says nothing at all about laser wavelengths and thus gives no guidance with regard to the 1200-1800 nm range recited in the appealed claims. Nor does Goldman say anything with regard to choice of chromophores and has no appreciation of the different chromophore characteristics of the tissues and fluids associated with varicose veins or of the importance of those chromophore characteristics in choosing a laser having a desirable wavelength.

Sinofsky, who discloses a preferred laser treatment of arterial plaque with laser energy in the range 1900-2100 nm (column 3, lines 15-19), also discusses the characteristics of various types of lasers and discloses tissue removal with laser energy in the range 1400-2200 nm (column 2, line 63). In fact, Sinofsky's discussion of lasers of different types with wavelengths ranging from 200-2200 nm at columns 2-4 makes it clear that the selection of a wavelength suitable for a given target must include not only the absorption characteristics of the target, but also the absorption characteristics of materials which are not the target but which are in the path of the laser energy, to avoid unacceptable energy loss before the energy reaches the target. These characteristics must be taken into account,

but the Goldman '084 patent failed to even recognize this need, much less enable the choice of laser, choice of wavelength, etc.

Dew et al. disclose the use of an Nd:YAG laser tuned from its normal wavelength of 1064 nm to its "secondary wavelength" of 1320 nm, col. 4, lines, 11-14, but not for varicose vein treatment and not for treatment of plaque, but rather for wound healing and tissue repair by solubilizing collagen. In addition, Dew's 1320 nm is outside Sinofsky's lower limit of 1400 nm, and Dew's range of 1200-1400 nm is adjacent to the 1400-2200 nm range of Sinofsky. There is no disclosure in Sinofsky of a Nd:YAG laser of any type and no disclosure of tuning such a laser to its secondary wavelength of 1320 nm. Thus, the wavelength choices in Sinofsky and Dew et al. are antithetical to each other, as are their respective targets, and these references cannot be properly or sensibly combined.

Based on this gallimaufry of references, the Examiner states at p. 15 of the Final Rejection:

> "It would have been obvious to the artisan of ordinary skill to employ the wavelength of Dew et al. in the method of Goldman et al ('084) wince Goldman ('084) teach no particular wavelength, and since the wavelength of Dew et al. can destroy (denature) the proteins, but allow near normal tissue to take it's (sic) place. (See Dew et al., column 11, lines 37-44) and since this wavelength is highly absorbed as taught by Sinofsky, thus producing a method such as claimed."

To state this proposition is to refute it. The notion that the failure of Goldman to provide any guidance with regard to wavelength leaves the Examiner free to pick any reference that discloses, for any purpose, a wavelength that comes within applicants' claimed range and combine it with Goldman demonstrates a very serious lack of reasoning and has no rational underpinning. Rather, the Examiner was motivated only by applicants' claims to attempt a reconstruction of applicant's

invention. To then toss Sinofsky into the pot for his teaching that plaque will absorb laser energy at 1400-2200 nm (column 5, lines 17-21) adds a reference which has nothing to do with Goldman (or Dew et al.) and operates in a range which is essentially different from and antithetical to that of Dew et al., a difference which stems from the fact that the purpose and the target of Sinofsky are entirely different from those of Dew et al.

Plainly, the Examiner has not made a prima facie case of obviousness by relying on such disparate references. In the time subsequent to the decision in KSR International v. Teleflex, Inc., 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), this Board has repeatedly recognized that rejections should be reversed when the Examiner fails to articulate reasoning with a rational underpinning for combining the prior art. For example, in Ex Parte Erkey et al., Appeal No. 20071375, decided May 11, 2007, this Board said:

> "We determine that the examiner has not provided a sufficient reason or explicit analysis of why the disclosures of the references should be combined."

Similarly, in Ex Parte Crawford et al., Appeal 20062429, decided May 30, 2007, this Board reversed a rejection and said:

> "We find no suggestion to combine the teachings and suggestions of [the references] as advanced by the examiner, except from using appellant's invention as a template through a hindsight reconstruction of appellant's claims."

We submit that the Examiner in the present case has done precisely the same thing as the Examiner in Crawford. Furthermore, it is important to note that KSR cited the decision in In Re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006) with approval. In Kahn, the Federal Circuit stated:

"[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."

In the present case, the Examiner has provided neither articulate reasoning nor a rational underpinning to support his rejection. Rather, he has used the silence in Goldman with regard to laser wavelength as a blank check in his effort to reconstruct the claimed invention by relying on the unrelated disclosures of Sinofsky and Dew et al.

Claims 3-5, 42 and 43 have been rejected as unpatentable under 35 U.S.C. § 103(a) over Goldman '084 in combination with Sinofsky, Dew and Roth. These claims recite a pull back device and Roth, in an entirely different context, also discloses a pull-back device. The most important point is that the Roth reference, which is directed to the treatment of benign prostate hypoplasia (BPH), does nothing to cure the deficiencies in the attempted combination of Goldman, Sinofsky and Dew et al. Furthermore, the Examiner provides no reasoning or rational underpinning for combining Roth with Goldman, Sinofsky and Dew et al. They are all directed to different fields of use. Thus, the rejection of these claims is in error.

Claims 8 and 39 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Goldman '084 in combination with Sinofsky, Dew, and Conn. Conn teaches a diffusing tip. Applicant does not purport to be an inventor of a diffusing tip for a laser and points out that Conn does nothing to cure the deficiency of the attempted combination of Goldman with Sinofsky and Dew. Furthermore, the Examiner has not provided reasoning or a rational underpinning for combining Conn with the remaining references. It is only an attempt to reconstruct applicants' invention which inspires reliance on Conn. Thus, claims 8 and 39 are patentable over the asserted combination of references.

Claims 9-13 have been rejected as unpatentable under 35 U.S.C. § 103(a) over Goldman in view of Sinofsky, Dew and Makower. These claims recite the use of a thermal sensor to maintain a

desired temperature. Makower discloses the use of infrared sensing to control heating of prostate tissue during the treatment of benign prostate hypoplasia. What is significant is that Makower does not cure any of the deficiencies in the attempted combination of Goldman with Sinofsky and Dew. Furthermore, once again, it is only an attempt re reconstruct applicants' invention which prompts citation of Makower. There is nothing in the remaining references to suggest that use of a temperature sensor is needed or desirable. The rejection of these claims is thus in error.

Claims 14-17 and 20-23 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Makower in combination with Roth and Dew. None of these references have anything to do with treatment of varicose veins. Makower and Roth are both directed to treatment of BPH and Roth discloses, at column 10, line 33, that the standard wavelength for an Nd:YAG laser is 1,064 nm. Makower discloses a Nd:YAG laser, but gives no information with regard to wavelength, so it is reasonable to read Makower as disclosing a standard Nd:YAG laser having a wavelength of 1064 nm. The notion that one skilled in the art interested in treating BPH as disclosed in Makower and Roth which explicitly or implicitly disclose the standard wavelength of 1,064 nm would have any interest in the secondary laser wavelength of Dew et al., which is used for an entirely different purpose, is simply untenable. Furthermore, Makower and Roth cannot be combined. Makower is directed to a device which has a "locking" means to prevent movement of his laser and all of the claims in Makower are limited to a locking means. Roth, on the other hand, wants to pull his laser device through the tissue which is incompatible with the locking system of Makower. Thus, this rejection is based on an absolutely improper combination of references. Furthermore, Dew et al. use a tuned Nd:YAG laser in order change it from its standard 1,064 nm wavelength to obtain the "secondary wavelength" of 1,320 nm for a use completely different from the treatment of BPH. See

col. 6, lines 11-18. There is absolutely nothing to suggest that either Makower or Roth would want to use the wavelength of Dew et al.

Claim 19 has been rejected under 35 U.S.C. § 103(a) as unpatentable over Makower in view of Dew, Roth and Conn. This is, if it is possible, an even more improper combination than that of Makower, Dew and Roth. Conn teaches a diffusing tip for a laser. There is nothing in any of Makower, Dew or Roth to suggest that they have any interest in a diffusing tip, that it would be useful in any of their devices or that one skilled in the art would have any inclination to use a diffusing tip in those devices. Thus, this rejection is also in error.

It is believed that the foregoing discussion establishes the reversibility of the Examiner's rejections. However, there is much more. Applicants have submitted several declarations during the course of prosecution which trace the real-world evolution of the treatment of varicose veins with energy and have pointed out the Navarro Patent No. 6,398,777 and its place in the evolution of varicose vein technology. We turn now to those considerations.

Navarro Patent No. 6,398,777

The Navarro patent is regarded by those in the art as representative of the early work done with regard to the use of lasers in treating varicose veins. It discloses the use of lasers which have wavelengths in the range of 500-1100 nm which target the hemoglobin in blood as a chromophore for these wavelengths.

The Adoption of Laser Technology

Prior to the present invention, all of the laser devices for patient treatment of varicose veins used lasers having wavelengths in the range of 810-980 nm. As shown in Exhibits A-E to the Hennings Declaration dated June 30, 2005, these devices were:

Exhibit A – Dorniter – 940 nm

Exhibit B – Biolitac – 980 nm

Exhibit C – AngioDynamics – 980 nm

Exhibit D – Vascular Solutions – 810 nm, 940 nm and 980 nm

Exhibit E – Diomed – 810 nm

Thus, the real world of laser treatment of varicose veins prior to the present invention constituted targeting hemoglobin as a chromophore and using wavelengths in the range of 810-980 nm. This is reflected in a survey article entitled *Endovenous laser ablation: mechanism of action* by Drs. Fan and Rox-Anderson which is attached as Exhibit 1 to the second Hennings Declaration dated December 22, 2008.

The Fan/Rox-Anderson article also describes, at page 208, the difference between the Navarro and other prior art wavelengths and that of the present invention as follows:

> "Hemoglobin and to a lesser extent myoglobin in vein wall smooth muscle components are the dominant chromophores at the lower end of this range [810, 940, 980 and 1064 nm], while at 1320 nm water dominates as the energy-absorbing molecule."

At page 209, the Fan/Rox-Anderson article describes the use of 1320 nm energy as follows:

> "Special consideration must be given to EVLA (endovenous laser ablation) with 1320 nm Nd:YAG laser. At this wavelength the dominant chromophore is water and, as the biological tissue is largely composed of water, deeper energy penetrance and photothermolytic effect can be achieved at lower fluence. Compared with 12-15 W power setting typically used during EVLA with 810-1064 nm wavelength light, EVLA at 5 W with the 1320 nm laser has been shown to be effective at 12-month follow-up for closing saphenous veins 12mm in diameter. At this higher wavelength and lower energy application, clinical evidence of perforation (pain, bruising) appears to be reduced."

Prior Art Taught Against the Use of Wavelengths Higher Than 1064 nm

At the time the present invention was made, it was the prevailing scientific view that the use of laser wavelengths above 1064 nm was undesirable. In addition to the fact that hemoglobin would no longer be a chromophore for wavelengths above 1064 nm, it was believed that, as reflected in Exhibits A, B and C to the Geriak Declaration dated November 22, 2005 that it would be disadvantageous to the patient to use wavelengths higher than 1064 nm.

As stated in the Minn et al. article, Exhibit A to the Geriak Declaration entitled *Endovenous Laser Treatment of Saphenous Vein Reflux: Long-Term Results* from the Journal of Vascular and Interventional Radiology, August 2003, pages 991-996, at page 995:

> "Published experience with endovenous laser with use of wavelengths other than 810 nm is limited. A recent study by Chang and Chua reported the use of 1064 nm laser energy delivered endovenously for treatment of GSV (greater saphenous vein) reflux. Although this study reported a success rate of 96.8% in 244 legs followed up to 28 months, significant complications were noted, including paresthesias (36.5%) and skin burns (4.8%).... In addition, patients treated with the 1064 nm wavelength underwent spinal or general anesthesia rather than strictly local tumescent anesthesia."

Thus, as the wavelength increased, additional "significant complications were noted" and, unlike treatment with lower wavelengths, spinal or general anesthesia was required rather than strictly local anesthesia.

Still further, at page 995, the Minn et al. article goes on to state:

> "In comparison, in our series of more than 500 limbs treated with 810 nm diode laser energy delivered endovenously, there have no heat related complications despite the high temperatures attained at the laser fiber tip. This may be explained by the following: (1) improved delivery and use of sufficient amounts of tumescent fluid in the proper tissue plane providing protective thermal 'sync'; (2) selected homogeneous and circumferential heating of the inner vein wall by absorption of 810 nm laser energy by blood lining the vein wall, as noted in a recent study by Proebstle et al., rather than deeper penetration of laser energy as

> less homogeneous heating from endovenous laser performed with wavelengths such as 1064 nm which are absorbed less by blood and more by water; and (3) faster rates of withdrawal and shallower depth of penetration of 810 nm laser energy resulting in less damage to surrounding nontarget tissue compared with methods that use RF."

The Proebstle article referred to in the Minn et al. article is Exhibit B to the Geriak Declaration and is entitled *Thermal Damage of the Inner Vein Wall During Endovenous Laser Treatment: Key Role of Energy Absorption by Intravascular Blood*, which appeared in Dermatologic Surgery, July 2002, pages 596-600. This article, e.g., at page 599, plainly teaches the desirability of using laser energy in the range 810-980 nm, e.g., at page 599, where it emphasizes that blood plays a "key role in absorption of 940 nm laser energy but also in absorption of 810 and 980 nm laser energy". Thus, the emphasis was on using wavelengths for which blood, not water, would be a chromophore.

Similarly, the Proebstle article attached to the Geriak Declaration as Exhibit C, which is entitled *Endovenous Treatment of the Greater Saphenous Vein With a 940 nm Diode Laser: Thrombotic Occlusion After Endoluminal Thermal Damage by Laser-Generated Steam Bubbles*, which appeared in Journal of Vascular Surgery, April 2002, pages 729-736, emphasizes the then prevailing view that it was important to target blood as the chromophore with a 940 nm wavelength laser.

The foregoing articles are, of course, consistent with the disclosure in the Navarro '777 patent. In addition, each of them cites to the Navarro article which appeared in Dermatological Surgery in 2001 in Volume 27 at pages 117-122 as the initial work in using lasers to treat varicose veins which was the basis for the Navarro '777 patent. These references are footnote 12 in Exhibit A

to the Geriak Declaration, footnote 3 in Exhibit B and footnote 8 in Exhibit C. This Navarro paper contains essentially the same disclosure as the Navarro '777 patent.

Thus, to recapitulate prior to the present invention, not only was blood (and the hemoglobin in blood) considered to be the proper choice of chromophore for treatment of varicose veins with laser wavelengths in the range 810-980 nm, but it was also the view of the prior art that treatment with wavelengths as high as 1064 nm was undesirable. This is confirmed by the 2008 survey article by Fan/Rox-Anderson which cites the Navarro '777 patent in footnote 15 as the earliest disclosure of laser treatment of varicose veins. Thus, the uniform view expressed in the scientific literature is that, prior to the present invention, there was no consideration of using anything other than blood as a chromophore for laser energy in the 810-980 nm wavelength range, and that a wavelength as high as 1064 nm was undesirable. The present invention was a substantial and significant departure from this prior art, i.e., targeting water as a chromophore with laser energy in the range 1200-1800 nm was demonstrably unobvious to the prior art.

Furthermore, subsequent to applicants' invention, at least one other worker has followed in their footsteps. *See* Paithankar, Published Application No. 2005/001523, filed June 30, 2004, based on a provisional application filed on June 30, 2003, which discloses the use of wavelength of 1160 nm to 2600 nm in the treatment of varicose veins. Paithankar confirms, in paragraphs 53 and 54, that using energy having the wavelengths claimed in the present application minimizes collateral damage to "tissues surrounding the target blood vessel."

The Examiner's Refusal to Consider the Evidence of Patentability

The Examiner has repeatedly refused to consider the evidence of patentability submitted by applicants. In the earlier final rejection dated February 12, 2007, the Examiner had the following to

say about the scientific literature and the activity of those in the real world of varicose vein treatment:

> "Applicant then posits that in the real world those attempting to use lasers 'to accomplish the purpose of Goldman' deliberately choose not to use applicants wavelengths. The examiner must respectfully disagree. Firstly, it is noted that the three articles submitted by applicants do not constitute a statistically significant sample of all the publications dealing with laser treatment of varicose veins and as such, cannot be the basis for a claim such as made by applicant. Secondly, the 'purpose of Goldman' is to heat the vessel wall {see, for example column 9, line 13}. The purposes of the articles submitted by applicant is (sic) is to heat the blood in the vessel. And, as clearly taught by Dew et al. and set forth above, this is achieved by employing wavelengths that are absorbed by the tissue that it is desired to be heated."

In the final rejection dated March 13, 2009, the Examiner seems to abandon the position taken in the final rejection dated February 12, 2007 and says the following with regard to the evidence of patentability:

> "It is important to note that the articles and product information were submitted with affidavits and that all affidavits only aver that the submissions are "true copies" of the articles or product literature which is described in the affidavits. There is no assertion whatsoever in any affidavit of record that the articles or product literature are in any way representative of the prior art with respect to varicose vein treatment. Instead such assertion are made only in the remarks accompanying the affidavits. This is interesting, given that these remarks bear the signature of Mr. Geriak one of the affiants. However, as these assertions are only submitted in the form of remarks accompanying a response, they cannot be elevated to the status of evidence. As such, these remarks are noted, but do not speak to the propriety of the combination which the examiner has applied to the claims."

The foregoing statement is remarkable in many respects, but the single most remarkable aspect of the Examiner's statement is the sentence which says "There is no assertion whatsoever in any affidavit of record that the articles or product literature are in any way representative of the prior art with respect to varicose vein treatment." Just the opposite is true.

In the Hennings Declaration dated December 22, 2008, after stating in paragraph 4 that Mr. Hennings has "30 years of experience in the design, development and use of laser-based devices for medical applications and 6 years of such experience with regard to lasers used for treatment of varicose veins", Mr. Hennings says, in paragraph 10:

> "Based on my own first-hand knowledge I can state unequivocally that the Examiner was incorrect in refusing, at page 11 of the Examiner's answer, to accept the assertions of our counsel, Mr. Geriak, that Exhibits A, B and C to his declaration were representative of the prior art. Furthermore, I believe that the Fan/Rox-Anderson article attached hereto is fully consistent with the fact that Exhibits A, B and C attached to the aforesaid Geriak declaration are representative of the prior art."

Similarly, in paragraph 8 of the Goldman Declaration dated December 23, 2008, Dr. Goldman states:

> "Our use of laser wavelengths in the range 1200-1800 nm as claimed in the present application was contrary to the view held by prior art workers that such wavelengths would be undesirable, a view expressed in the Minn and Proebstle articles which are attached to the Geriak declaration as Exhibits A, B and C and which are representative of the belief held by the prior art prior to the invention claimed in this application."

Thus, the Examiner's assertion that there are no such declarations of record in the present application is profoundly erroneous.

The Examiner's earlier statement in the final rejection dated February 12, 2007 that the articles attached as Exhibits A, B and C to the Geriak Declaration do not constitute a "statistically significant sample" of "all the publications dealing with laser treatment of varicose veins" is not only seriously misguided and unsupported by identification of any other such publications, it is also at odds with the Fan/Rox-Anderson survey article attached as Exhibit 1 to the Hennings Declaration dated December 22, 2008. That article cites to the two Proebstle articles, Exhibits B and C to the Geriak Declaration, in footnotes 7 and 14. This is a powerful demonstration that the Proebstle

articles are fully representative of the prior art. In addition, the Fan/Rox-Anderson article also cites two articles from the Journal of Vascular and Interventional Radiology in footnotes, 12, 21 and 22 which is the same journal in which the Minn article attached as Exhibit A to the Geriak Declaration appeared. There are no articles cited in the Fan/Rox-Anderson survey article which in any way contradict or express a view contrary to the view expressed in Exhibits A, B and C to the Geriak Declaration. Thus, there is absolutely no basis for the notion that those articles are "not statistically significant". Furthermore, from a statistics perspective, if all of the articles on a given subject agree, they are indeed statistically significant.

In addition, the Examiner's position statement at pages 19 and 20 of the final rejection dated March 13, 2009 takes on a surreal quality when compared with the Examiner's statement at page 2 of that final rejection that "In paragraph 6, declarant (Hennings) asserts that the scientific literature attached to the Geriak declaration 'are fully representative of the prior art with respect to varicose vein treatment." And the Examiner's statement at page 4 that "In paragraph 10, declarant (Hennings) asserts that 'I can state unequivocally that the Examiner was incorrect in refusing, at page 11 (sic 9) of the Examiner's answer, to accept the assertions of our counsel, Mr. Geriak, that Exhibits A, B and C to his Declaration were representative of the prior art.'" is equally at odds with his position statement on pages 19 and 20. Thus, although the existence of any such declarations is denied on page 19 of the final rejection, there is a recognition on pages 2 and 4 that such declaration statements do exist. Then, to compound matters, the Examiner goes on to say at page 4 of the final rejection that "Declarant's (Hennings) statement is simply opinion testimony." Factual statements such as those made by Mr. Hennings cannot be blithely wished away by characterizing them as "opinion". The Hennings statements are fact, not opinion, and are not contradicted by anything in the record.

Indeed, the Examiner acknowledges at pages 5 and 6 that the Fan/Rox-Anderson article is consistent with the articles which are exhibits to the Geriak Declaration being representative of the prior art.

Furthermore, at page 8 of the final rejection, the Examiner discusses paragraph 8 of the Goldman Declaration but entirely fails to recognize the statement in that paragraph that Exhibits A, B and C to the Geriak Declaration are representative of the prior art.

Thus, the Examiner has variously denied the existence of the Hennings and Goldman Declarations (page 19), recognized the statements in paragraphs 6 and 10 of the Hennings Declaration at pages 2 and 4 of the final rejection, but dismissed them as "simply opinion testimony" at page 4 of the final rejection and has ignored the same statement regarding representative prior art in paragraph 8 of the Goldman Declaration at page 8 of the final rejection. This head-spinning inconsistency in the final rejection defies explanation.

Thus, the final rejection falls far short of the standard set forth in In Re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006) that:

> "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead there most be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."

Here, there is just the opposite. The Examiner's statement of his positions is inconsistent and those positions are all over the lot. Furthermore, those positions cannot be read other than as a flat-out refusal to give effect to the evidence of patentability submitted by the applicants. Such a refusal is directly contrary to law as set forth in In Re Sullivan, 498 F.3d 1345, 84 USPQ2d 1034 (Fed. Cir. 2007) which held that evidence submitted by a patent applicant must be given meaningful consideration. Furthermore, as noted in In Re Sullivan, at 498 F.3d 1351, evidence "that the prior art teaches away from the claimed invention in any material respect is probative evidence of

unobviousness." Similarly, the decisions in In Re Haruna, 249 F.3d 1327, 1335 (Fed. Cir. 2001) and in Tec Air, Inc. v. Denso Mfg. Co., 192 F.3d 1353, 1360 (Fed. Cir. 1999) state that:

> "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, ... would be led in a direction divergent from the path that was taken by the applicant."

This is precisely the situation presented in this appeal in which the applicants diverged both with regard to chromophore targets and laser wavelengths from the path taken by the prior art. This is compelling rebuttal evidence of patentability. However, the Examiner has utterly failed to comply with the requirement of Sullivan at 498 F.3d 1351 that:

> "When a patent applicant puts forth rebuttal evidence, the Board must consider that evidence. *See* In Re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995.)"

In Sullivan, the Court remanded the case to the Board. In the present case, it is respectfully submitted that the deficiencies in the Examiner's rejections, even without his refusal to consider the evidence of patentability set forth in the declarations, mandate a reversal of the Examiner's rejections and that the evidence of patentability which has been submitted would overwhelmingly refute a prima facie showing of obviousness if such a showing had been made. Thus, it is believed that reversal of the Examiner's rejections is appropriate.

Conclusion

The claims in the present application are directed to an invention which is plainly patentable over the prior art. It is respectfully submitted that a reversal of each of the rejections is appropriate.

Request for Oral Hearing

Applicant hereby requests that an Oral Hearing be scheduled in this application. The Commissioner is hereby authorized to charge any fees associated to Deposit Account No. 15-0665.

Fees

The Commissioner is authorized to charge Orrick's Deposit Account No. **15-0665** for any fees required and credit any overpayments to said Deposit Account No. **15-0665**.

Respectfully submitted,

Orrick, Herrington & Sutcliffe, LLP

Dated: September 11, 2009

By: 

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APPENDIX 1

APPENDIX

1. An endovenous method of treating a varicose veins comprising the step of using a laser having a wavelength between about 1.2 and about 1.8 um to heat and shrink collagen in a varicosed vein and to destroy the functionality of the varicose vein.

2. The method of claim 1 in which the laser energy is delivered with a fiber optic laser delivery device.

3. The method of claim 1 further comprising the following steps:

inserting a fiber optic laser delivery device into the varicose vein;

using a pullback device to retract the fiber optic laser delivery device through the varicose vein at a rate of between about 0.1 mm/sec and about 10.0 mm/sec while simultaneously delivering laser energy therefrom.

4. The method of claim 3 in which the fiber optic laser delivery device is retracted at a rate of between about 1.0 mm/sec and about 5.0 mm/sec.

5. The method of claim 3 in which the pullback device begins retraction of the fiber optic laser delivery device just prior to initiating delivery of the laser energy, thereby preventing the tip of the fiber, optic laser delivery device from sticking to the vessel wall.

6. The method of claim 1 further comprising the preliminary step of removing blood from the varicosed vein prior to treatment with laser energy.

7. The method of claim 2 in which the fiber optic laser delivery device is introduced to the varicose vein through an introducer catheter.

8. The method of claim 2 in which the energy delivered through the fiber optic laser delivery device is evenly distributed by using a diffuse radiating-tip mounted to the distal end of the fiber optic laser delivery device.

9. The method of claim 2 in which an non-contact thermal sensor is used to maintain a desired temperature.

10. The method of claim 9 in which the thermal sensor is used to maintain a desired coagulation temperature.

11. The method of claim 9 in which the thermal sensor is used to maintain a desired collagen shrinkage temperature.

12. The method of claim 2 further comprising the step of using the fiber optic laser delivery device as a thermal sensing element.

13. The method of claim 9 further comprising the step of modulating the laser power based on the sensed temperature to maintain the desired temperature.

14. A system for endovenous treatment of varicose veins comprising the following:

a laser having a wavelength between about 1.2 and about 1.8 um; and

a fiber optic laser delivery device having a proximal end and a distal end, for delivery of laser energy from the distal end of the fiber optic laser delivery device to the inside wall of a varicose vein wherein the functionality of the varicose vein is destroyed and collagen in the varicosed vessel wall can be heated and shrunk.

15. The system of claim 14 further comprising a pullback device which retracts the fiber optic laser delivery device through the varicose vein at a rate of between about 0.1 mm/sec and about 10.0 mm/sec.

16. The system of claim 14 further comprising means for administration of anesthesia to tissue surrounding the varicose vein, wherein the anesthesia causes swelling of the tissue surrounding the varicose vein which causes compression of the varicose vein in order to remove blood prior to treatment.

17. The system of claim 14 further comprising an introducer catheter in which an elongated lumen portion has a proximal end and a distal end, wherein the fiber optic laser delivery device is introduced to the introducer catheter through the proximal end and is introduced to the varicose vein through the distal end.

18. (cancelled)

19. The system of claim 17 further comprising a diffusing tip at the distal end of the introducer catheter for providing even distribution of energy radiating during treatment.

20. The system of claim 17 further comprising a diffusing tip at the distal end of the fiber optic laser delivery device for providing even distribution of energy radiating during treatment.

21. The system of claim 14 further comprising an non-contact thermal sensor.

22. The system of claim 21 further comprising a controller coupled to the thermal sensor for controlling the temperature in a region near the distal end of the fiber optic laser delivery device.

23. The system of claim 22 in which the controller modulates a power input to the laser for controlling the temperature in a region near the distal end of the fiber optic laser delivery device.

24. (cancelled)

25. An endovenous method of treating varicose veins with laser energy to heat and shrink collagen in the vein and to destroy the functionality of the varicosed vein, the method comprising the following steps:

inserting a laser delivery device into the varicose vein;

delivering laser energy having a wavelength between about 1.2 and about 1.8 um to the varicose vein; and

retracting the laser delivery device through the varicose vein, thereby heating and shrinking the collagen in the vein and destroying the functionality of the varicose vein.

26. The method of claim 1 wherein the laser has a wavelength of about 1.32 um.

27. The system of claim 14 wherein the laser has a wavelength of 1.32 um.

28. The method of claim 25 wherein the laser energy has a wavelength of about 1.32. um.

29. The method of claim 1 wherein said laser is a Nd:YAG laser.

30. The system of claim 14 wherein said laser is a Nd:YAG laser.

31. The method of claim 25 wherein said laser is a Nd:YAG laser.

32. The method of claim 1 wherein the laser energy preferentially heats the water in the wall of the vein.

33. The system of claim 14 wherein the laser is adapted to preferentially heat water.

34. The method of claim 25 wherein the laser energy preferentially heats the water in the wall of the vein.

35. A method of treating varicose veins, comprising:

providing a beam of light comprising a wave length in the range of about 1200 nm to about 1800 nm; and

delivering endovascularly the beam of light to target a chromophore comprising water in the wall of a targeted varicose vein to treat the vein.

36. (Cancelled)

37. The method of claim 1 wherein said wave length is about 1320 nm.

38. The method of claim 35 further comprising delivering the beam of light via an optical fiber.

39. The method of claim 38 further comprising delivering the beam of light through a diffusing tip connectable to the optical fiber.

40. The method of claim 35 wherein the treatment comprises reducing the size of the targeted varicose vein.

41. The method of claim 1 further comprising heating the target chromophore to a temperature not greater than about 85° C.

42. (previously presented) The method of claim 38 wherein a pull-back device is used to position the optical fiber.

43. The method of claim 42 wherein the pull-back device withdraws the optical fiber from the targeted varicose vein at a rate of between about 0.1 mm/sec. and about 10.0 mm/sec.

44. The method of claim 35 in which blood is removed from the varicose vein prior to treatment with the beam of light.

45. The method of claim 35 wherein the beam of light has a power between about 1 to about 20 watts.

46. The method of claim 45 wherein the beam of light has a power of about 5 watts.

APPENDIX 2

IDS REFERENCES

☐ FOR

Endovenous Laser Treatment of Saphenous Vein Reflux: Long-Term Results

Robert J. Min, MD, Neil Khilnani, MD, and Steven E. Zimmet, MD

PURPOSE: To report long-term follow-up results of endovenous laser treatment for great saphenous vein (GSV) reflux caused by saphenofemoral junction (SFJ) incompetence.

MATERIALS AND METHODS: Four hundred ninety-nine GSVs in 423 subjects with varicose veins were treated over a 3-year period with 810-nm diode laser energy delivered percutaneously into the GSV via a 600-μm fiber. Tumescent anesthesia (100–200 mL of 0.2% lidocaine) was delivered perivenously under ultrasound (US) guidance. Patients were evaluated clinically and with duplex US at 1 week, 1 month, 3 months, 6 months, 1 year, and yearly thereafter to assess treatment efficacy and adverse reactions. Compression sclerotherapy was performed in nearly all patients at follow-up for treatment of associated tributary varicose veins and secondary telangiectasia.

RESULTS: Successful occlusion of the GSV, defined as absence of flow on color Doppler imaging, was noted in 490 of 499 GSVs (98.2%) after initial treatment. One hundred thirteen of 121 limbs (93.4%) followed for 2 years have remained closed, with the treated portions of the GSVs not visible on duplex imaging. Of note, all recurrences have occurred before 9 months, with the majority noted before 3 months. Bruising was noted in 24% of patients and tightness along the course of the treated vein was present in 90% of limbs. There have been no skin burns, paresthesias, or cases of deep vein thrombosis.

CONCLUSIONS: Long-term results available in 499 limbs treated with endovenous laser demonstrate a recurrence rate of less than 7% at 2-year follow-up. These results are comparable or superior to those reported for the other options available for treatment of GSV reflux, including surgery, US-guided sclerotherapy, and radiofrequency ablation. Endovenous laser appears to offer these benefits with lower rates of complication and avoidance of general anesthesia.

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Abbreviations: GSV = great saphenous vein, RF = radiofrequency, SFJ = saphenofemoral junction

LOWER-extremity venous insufficiency is a common medical condition afflicting 25% of women and 15% of men in the United States (1). Gender, pregnancy, hormones, aging, and gravitational forces from prolonged standing or sitting are the most common factors that influence the appearance or worsening of primary varicose veins (2,3). Although many people seek medical treatment for varicose veins because they find them unsightly, most people with varicose veins do experience symptoms (4,5). Unfortunately, symptoms of primary venous insufficiency are often not recognized by patients or their physicians. Characteristic leg complaints associated with varicose veins include aching pain, night cramps, fatigue, heaviness, or restlessness. Symptoms arise from pressure on somatic nerves by dilated veins and are typically worsened with prolonged standing, during the premenstrual period, or in warm weather (6). Left untreated, nearly 50% of patients with significant superficial venous insufficiency will eventually experience chronic venous insufficiency characterized by lower-extremity swelling, eczema, pigmentation, hemorrhage, and ulceration (7).

Great saphenous vein (GSV) reflux is the most common underlying cause of significant varicose veins. Traditional treatment of GSV reflux has been surgical removal of the GSV. Al-

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R.J.M. is a consultant to Diomed (Andover, MA), assisting in development of medical treatments and physician training. R.J.M. is coinventor and part owner of a patent on endovenous laser treatment of veins, for which he receives royalties. R.J.M. and Cornell Vascular have paid for all medical equipment used in procedures relating to this study. S.E.Z. is a paid consultant to Diomed, Inc. (Andover, MA), assisting in development of medical treatments. S.E.Z. is also paid to assist in physican training. S.E.Z. purchased all medical equipment he used in connection with this study. The other author has not identified a potential conflict of interest.

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though surgical ligation and stripping of the GSV has been the most durable treatment, it is associated with significant perioperative morbidity. Less-invasive surgical treatments including high ligation of the GSV at the saphenofemoral junction (SFJ) have been attempted with the hope that gravitational reflux would be controlled while the vein is preserved for possible use as a bypass graft. Unfortunately, ligation of the GSV alone usually results in recurrent varicose veins (8). Even when high ligation has been combined with phlebectomy of varicose tributaries or retrograde sclerotherapy, recurrence has been the rule (9,10). Therefore, when it is determined that GSV reflux is the principal underlying problem, treatment should involve eliminating this source of reflux with ablation of any associated incompetent venous segments.

In 1999, Boné (11) first reported on delivery of endoluminal laser energy. Since then, a method for treating the entire incompetent GSV segment has been described (12,13). Endovenous laser treatment, which received approval from the US Food and Drug Administration in January 2002, allows delivery of laser energy directly into the blood vessel lumen. Nonthrombotic vein occlusion is accomplished by heating the vein wall with 810-nm-wavelength laser energy delivered via a 600-μm laser fiber (Diomed, Andover, MA). Sufficient heating of the vein wall is necessary to cause collagen contraction and denudation of endothelium. This stimulates vein wall thickening, eventual luminal contraction, and fibrosis of the vein. The purpose of this study is to report on the long-term follow-up results of endovenous laser treatment for GSV reflux.

MATERIALS AND METHODS

This prospective, nonrandomized, consecutive-enrollment study included 423 patients who underwent endovenous laser treatment of incompetent GSV segments with 810-nm diode laser energy delivered intraluminally for treatment of primary varicose veins. The study protocol was approved by the Weill Medical College of Cornell University Institutional Review Board. All patients gave written informed consent before treatment.

Patient Selection

Directed history and physical examination, including duplex ultrasound (US) evaluation of the superficial venous system, was performed on limbs of subjects with varicose veins. Study inclusion criteria included varicose veins caused by SFJ incompetence with GSV reflux as demonstrated by duplex US imaging, age of at least 18 years, and ability to return for scheduled follow-up examinations for 12 months after endovenous laser treatment. Exclusion criteria included nonpalpable pedal pulses; inability to ambulate; deep vein thrombosis; general poor health; pregnancy, nursing, or plans to become pregnant during the course of participation in the investigation; and extremely tortuous GSVs that would not allow endovenous catheterization and passage of the laser fiber as identified on pretreatment venous duplex US mapping. After initial consultation and evaluation, subjects meeting the appropriate criteria were offered surgery versus endovenous laser treatment. Nearly all subjects chose endovenous laser over surgical ligation and stripping.

Five hundred four incompetent GSVs were treated with endovenous laser over a 39-month period. Five limbs were lost to follow-up. The remaining 499 limbs in 423 patients comprise the study population. This group consists of 352 women (83%) and 71 men (17%) ranging in age from 23 to 72 years, with a mean age of 42 years.

Follow-up ranged from 1 month to 39 months with a mean follow-up period of 17 months and an SD of 11 months. Aching leg pain was the most common presenting symptom, found in 87% of limbs. Overall, slightly more left legs (n = 263, 53%) were treated, and 76 patients (18%) were treated for bilateral GSV reflux. Pretreatment GSV diameter, measured in the upright position approximately 2 cm below the SFJ, ranged from 4.4 mm to 29 mm (mean, 11 mm; SD, 4.2 mm).

None of the patients in this series underwent concomitant ambulatory phlebectomy. All but seven patients underwent compression sclerotherapy treatment of distal varicose tributaries or associated telangiectasias at follow-up visits.

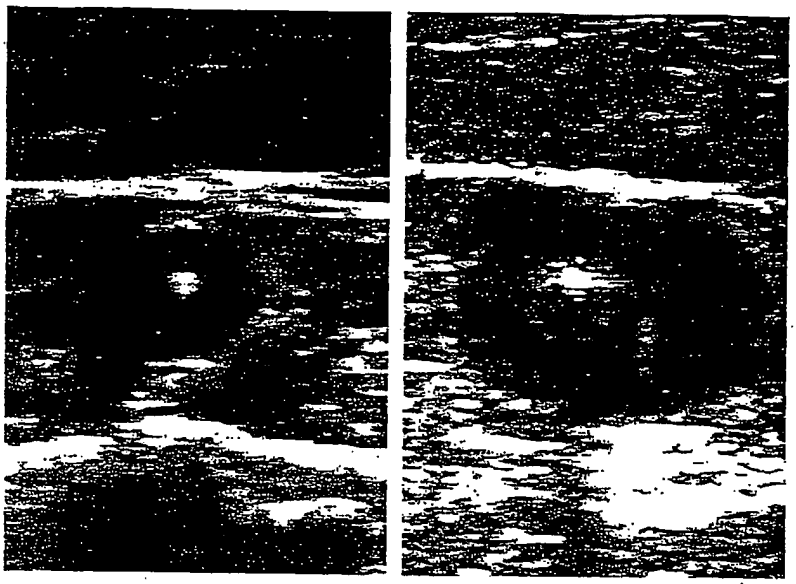
Description of Technique

Duplex US was performed in the upright position to map incompetent sources of venous reflux and then to mark the skin overlying the incompetent portion of the GSV starting at the SFJ. After venous duplex mapping, a percutaneous entry point was chosen. This point may be where reflux is no longer seen or where the GSV becomes too small to access (usually just above or below knee level). With use of local anesthesia and sonographic guidance, the GSV was punctured. A 5-F introducer sheath was placed into the GSV over a guide wire and advanced past the SFJ into the femoral vein. Intraluminal position within the GSV was confirmed by aspiration of nonpulsatile venous blood and visualization with US.

The sheath was flushed and a 600-μm laser fiber (Diomed) was inserted in the sheath and advanced up to the first site mark, indicating that the distal tip of the laser fiber was flush with the end of the sheath. The sheath was then withdrawn to the second site mark, exposing the distal 3 cm of the bare-tipped laser fiber. The sheath and fiber were pulled back together and positioned at the SFJ under US guidance. Position was confirmed by direct visualization of the red aiming beam of the laser fiber through the skin.

Tumescent local anesthesia consisting of 100–200 mL of 0.2% lidocaine neutralized with sodium bicarbonate, was administered along the perivenous space with use of US guidance. In addition to the anesthetic effects, properly delivered, this fluid serves two important functions: (1) it compresses and reduces the diameter of even the largest veins to provide vein wall apposition around the fiber tip with subsequent circumferential heating of the vein wall and (2) it provides a "heat sink" to minimize the possibility of heat-related damage to adjacent tissues. Figure 1a demonstrates the typical transverse sonographic appearance of the laser fiber and catheter seen centrally within an enlarged GSV located in the saphenous space. Proper and adequate delivery of tumescent anesthesia should result in fluid surrounding a compressed GSV as shown in Figure 1b.

The tip of the laser fiber was repo-



a. b.

Figure 1. Duplex US (transverse view) demonstrating appearance of the GSV before and after proper delivery of tumescent anesthesia. (a) Intraluminal position of laser fiber and catheter within an enlarged GSV; (b) tumescent anesthesia delivered by echogenic needle tip adjacent to laser fiber and catheter with fluid surrounding the compressed GSV.

sitioned within the GSV 5–10 mm distal to the SFJ. Tip position was checked by US and direct visualization of the red aiming beam through the skin. Laser energy (810-nm diode laser; Diomed) was delivered at 14 W in continuous mode. The vein was treated from 5–10 mm below the SFJ to approximately 1 cm above the skin entry site. Length of GSV treated with endovenous laser ranged from 10 cm to 55 cm (mean, 35 cm; SD, 10 cm). The laser fiber was withdrawn at an average rate of 3 mm per second (18 cm per minute). Of patients treated with 14-W continuous mode (n = 276, or 55% of limbs), delivery of laser energy ranged from 25 seconds (at 358 J) to 187 seconds (at 2,615 J), with a mean of 123 seconds (SD, 47 sec) or 1,727 J (SD, 650 J).

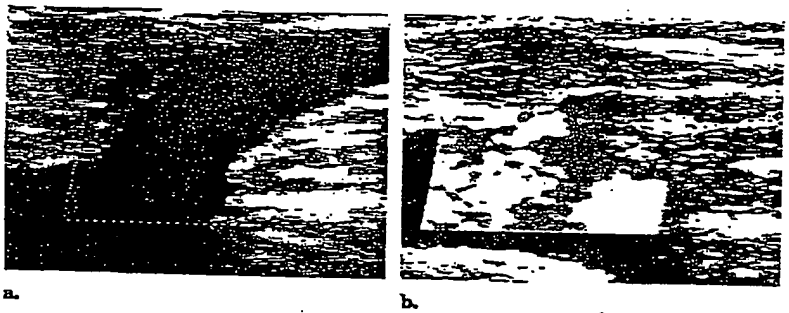
A class II (30–40 mm Hg) full-thigh graduated support stocking or panty hose was worn for at least 1 week at all times except to sleep or to shower. Patients were instructed to ambulate and resume their normal daily activities immediately. Clinical and duplex US follow-up was obtained at 1 week, 1, 3, 6, 9, and 12 months, and then yearly.

Compression sclerotherapy treatment of distal varicose tributaries was performed with use of sodium tetradecyl sulfate (0.3%–1% concentration). A detailed description of sclerotherapy technique is beyond the scope of this article but the approach used was the "French school" originally advocated by Tournay and more recently popularized in the United States by Goldman and other phlebologists (14). This technique relies on starting from the highest points of reflux and proceeding downward, and treating veins from the largest to the smallest. Compression stockings or panty hose were worn for at least 1 week after sclerotherapy treatments except to sleep or shower. Sclerotherapy treatments were performed at 4-week intervals, starting 1 month after endovenous laser ablation of the GSV.

Study Endpoints and Definitions

Duplex US criteria for successful treatment were the following: at 1-week follow-up, an enlarged noncompressible GSV, minimally decreased in diameter, with echogenic, thickened vein walls, and no flow seen within the occluded vein lumen on color Doppler interrogation; at 3- and 6-month follow-up, an occluded GSV with substantial (>50%) reduction in diameter; and at 1 year and beyond, complete disappearance of the GSV or minimal residual fibrous cord with no flow detectable. It is important to note that the expected appearance 1–2 weeks after endovenous laser is a slightly smaller GSV demonstrating wall thickening with absence of flow within the treated vein segment. The vein lumen is usually obliterated by the thickened wall, which has low-level echoes and is incompressible. This wall thickening should be differentiated from acute GSV thrombosis wherein the vein is also incompressible but the lumen is filled with anechoic acute thrombus. Several weeks after successful endovenous laser treatment, resolution of the acute inflammation in the vein wall should result in reduction in vein diameter. After several months, most of the treated vein segments will fibrose and be difficult to identify. Alternatively, superficial thrombophlebitis with GSV thrombus would result in recanalization of the vein. A longitudinal view of an enlarged, incompetent GSV is seen in Figure 2a. Figure 2b demonstrates the typical color Doppler appearance of a successfully treated GSV 1 year after endovenous laser treatment.

Clinical evaluation was performed on all subjects at 1 week, 1, 3, 6, 9, and 12 months, and yearly thereafter by the same physician (R.M.) who performed all the endovenous laser procedures. Patients were queried about symptomatic relief at follow-up visits, particularly improvement or resolution of lower-extremity pain believed to be associated with venous insufficiency. Improvement in the appearance of the leg, including reduction in visible varicosities, swelling, pigmentation, or other skin changes secondary to chronic venous insufficiency, were assessed by the patient and with direct comparison with pretreatment photographs obtained from all subjects undergoing treatment. Patients were evaluated for possible adverse reactions caused by endovenous laser treatment at each follow-up visit. Minor complications were defined as those that had no significant clinical sequelae, such as bruising. Major complications were defined as those necessitating an increased level of care, sur-



a. b.

Figure 2. Color Doppler examinations (longitudinal views) of the GSV at the SFJ demonstrating successful occlusion after endovenous laser treatment. (a) Pretreatment evaluation demonstrates an enlarged GSV with reflux after distal calf compression; (b) 1-year follow-up examination shows typical "cul-de-sac" appearance of the proximal GSV with occlusion of the treated segment.

gery, hospitalization, or permanent adverse sequelae.

RESULTS

Follow-up results ranging from 1 month to 39 months (mean, 17 months; SD, 11 months) were obtained in 499 of the 504 limbs treated with endovenous laser during the study period. Successful endovenous laser treatment, as defined earlier, was seen in 490 of 499 limbs (98%) at 1-month follow-up. Eight of nine GSVs requiring repeat endovenous laser were successfully closed with a second endovenous laser treatment. Continued closure of the treated GSV segments was noted at longitudinal follow-up at the following rates: 444 of 447 (99.3%) at 3 months, 390 of 396 (98.5%) at 6 months, 351 of 359 (97.8%) at 9 months, 310 of 318 (97.5%) at 1 year, and 113 of 121 (93.4%) at 2 years. Forty subjects have been followed for 3 years and no new recurrences were seen at 2 or 3 years that were not present at 1-year follow-up. In fact, all recurrences were noted before 9 months, with the majority seen by 3 months. This may indicate that these were not true recurrences but rather inadequate initial treatments.

Clinical examination correlated well with duplex US findings. All patients showed improvement in the appearance of the limb with disappearance or reduction in the size and number of visible varicosities. The typical appearance of varicose veins caused by incompetence of the SFJ with GSV reflux is shown in Figure 3a. One month after endovenous laser treatment, relief of symptoms and significant improvement in the appearance of the varicose veins was noted (Fig 3b). By 6 months after initial treatment, pain was greatly improved or resolved in all treated limbs. Although symptomatic resolution and significant improvement in the appearance of the leg is usually noted after endovenous laser treatment alone, most patients will need additional complementary procedures (ie, sclerotherapy or phlebectomy) to fully realize the restorative benefits of treatment.

Bruising outside the puncture site was noted in 24% of limbs at 1-week follow-up. Bruising resolved in all subjects before 1-month follow-up. Ninety percent of subjects felt a delayed tightness peaking 4–7 days after laser treatment and lasting 3–10 days. This sensation, described as "pulling" along the course of the treated GSV, was not felt in the nine patients in whom initial treatment failed. Five percent of patients developed superficial phlebitis of varicose tributaries after endovenous laser occlusion of the GSV. Most cases required no treatment. Symptomatic patients were treated with graduated compression stockings and over-the-counter antiinflammatory agents. All minor complications listed earlier resolved without sequelae. There have been no skin burns, paresthesias, cases of deep vein thrombosis, or other minor or major complications. The procedure was well-tolerated by all subjects with strictly local anesthesia.

Overall treatment satisfaction was determined by asking subjects if they would recommend the procedure to a friend with similar leg vein problems, and 422 of 423 subjects (99.8%) indicated they would recommend the procedure.

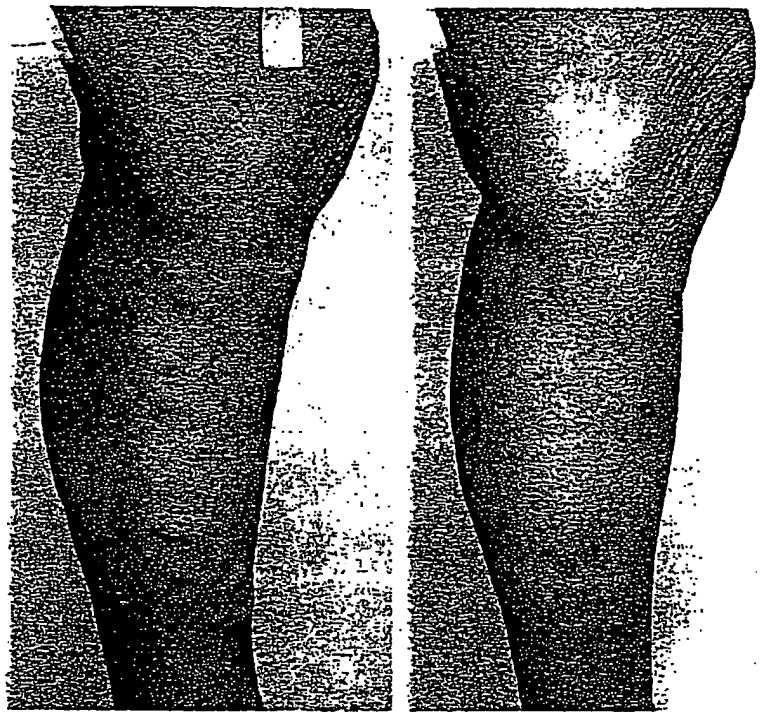
DISCUSSION

Percutaneous methods for treating incompetent GSVs are not new. Duplex-guided sclerotherapy for treatment of GSV reflux has been attempted, but long-term studies have failed to prove durability comparable to surgery (15–19). Initial attempts at damaging vein walls by electrocoagulation involved creation of a thrombus within the vessel lumen, ultimately resulting in recanalization (20–22). Early methods of intraluminal delivery of high-frequency alternating-current radiofrequency (RF) energy to treat GSV reflux were complicated by skin burns, saphenous nerve and peroneal nerve injury, phlebitis, and wound infection (23).

A more modern technique of the use of RF energy to eliminate saphenous vein reflux has been developed by VNUS Medical Technologies (Sunnyvale, CA). Early results reported from a multicenter trial demonstrated a reasonable degree of success with an overall failure rate of 10% at a mean follow-up of 4.7 months (13% in patients treated with RF alone and 5% in patients treated with RF plus high ligation of the GSV). Complications included transient paresthesias (thigh, 9%; leg, 51%), skin burns (3%), deep venous thrombosis (3%), and one pulmonary embolus (24). More recent studies have demonstrated success rates of 73%–90% with follow-up to 24 months in 21 limbs (25–27).

One of the limitations of our study is that it does not provide a blinded, randomized comparison of the various modern percutaneous methods available for treatment of GSV reflux, including RF and wavelengths of laser energy other than 810 nm. However, review of the literature allows some comparisons and raises some interesting areas for future study.

RF current damages tissue by resistive heating of structures in direct con-



a. b.

Figure 3. Significant improvement in appearance of varicose tributaries after endovenous laser treatment of an incompetent left GSV. (a) Typical appearance of varicose veins caused by GSV reflux; (b) the same leg 1 month after endovenous laser treatment.

tact with the electrodes. Deeper tissue planes are heated by conduction into normothermic tissue. Because the potential for heating of adjacent perivenous tissue is high, safe treatment with RF depends on proper delivery of adequate tumescent anesthesia. Effective use of tumescent anesthesia appears to have reduced the incidence of heat-related complications. In expert hands, the incidence of paresthesias after RF has occurred in as few as 8.5% of limbs within 1 week of treatment and decreased to 0.7% at 6 months (27). However, with less-experienced physicians, RF still has been complicated with heat-related adverse effects such as paresthesias (10% at 6 months) and skin burns (3.3%) (25).

Published experience with endovenous laser with use of wavelengths other than 810 nm is limited. A recent study by Chang and Chua (28) reported the use of 1,064-nm laser energy delivered endovenously for treatment of GSV reflux. Although this study reported a success rate of 96.8% in 244 legs followed up to 28 months, significant complications were noted, including paresthesias (36.5%) and skin burns (4.8%). In addition to endovenous laser ablation, all patients in their study underwent surgical ligation and division of the proximal and distal ends of the treated GSV. In addition, patients treated with the 1,064-nm wavelength underwent spinal or general anesthesia rather than strictly local tumescent anesthesia (28).

In comparison, in our series of more than 500 limbs treated with 810-nm diode laser energy delivered endovenously, there have been no heat-related complications despite the high temperatures attained at the laser fiber tip. This may be explained by the following: (1) improved delivery and use of sufficient amounts of tumescent fluid in the proper tissue plane providing a protective thermal "sink;" (2) selective, homogeneous, and circumferential heating of the inner vein wall by absorption of 810-nm laser energy by blood lining the vein wall, as noted in a recent study by Proebstle et al (29), rather than deeper penetration of laser energy and less-homogeneous heating from endovenous laser performed with wavelengths such as 1,064 nm, which are absorbed less by blood and more by water; and (3) faster rates of withdrawal and shallower depth of penetration of 810-nm laser energy, resulting in less damage to surrounding nontarget tissue compared with methods that use RF.

It has been suggested that a randomized controlled trial comparing outcomes of endovenous laser ablation of the saphenous vein to surgical ligation and stripping should be performed; however, such a study would be difficult given patients' overwhelming desire for minimally invasive treatments rather than surgery. Review of the existing surgical literature does provide some insight in assessing treatment durability. Multiple studies have shown that recurrence of varicose veins after GSV stripping occurs early (30), with 73% of limbs destined for recurrent varicosities at 5 years already having them at 1 year (31,32). Our results with endovenous laser have supported this, demonstrating that what is found on duplex imaging early is predictive of what will be seen later, with none of the treated patients developing recanalization of successfully occluded GSVs at 2 or 3 years that was not seen before 9 months.

Performing endovenous ablation of the GSV without dissection of the SFJ violates a cardinal rule in saphenous vein surgery that each of the tributaries must be individually divided. Surprisingly, the combined experiences with transcatheter endovenous ablation procedures have shown lower recurrence rates than with surgical ligation and stripping. Perhaps minimizing dissection in the groin and preserving venous drainage in normal, competent tributaries while removing only the abnormal refluxing segments does not incite neovascularization.

The understanding of venous disorders continues to improve with tremendous strides being made over the past decade. Readily available noninvasive diagnostic tests allow physicians to precisely map out abnormal venous pathways and identify sources of incompetence. Modern percutaneous methods of sealing incompetent veins

provide patients with alternatives to ligation and stripping for treatment of GSV reflux without the familiar morbidities associated with surgery (33,34). Given these recent advances, many physicians, when properly trained, will now be able to successfully diagnose and treat the whole spectrum of superficial venous insufficiency, offering acceptable options to the millions of people in the United States alone who have varicose veins but are unwilling or unable to undergo surgery.

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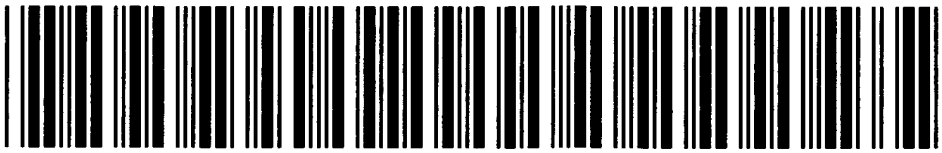

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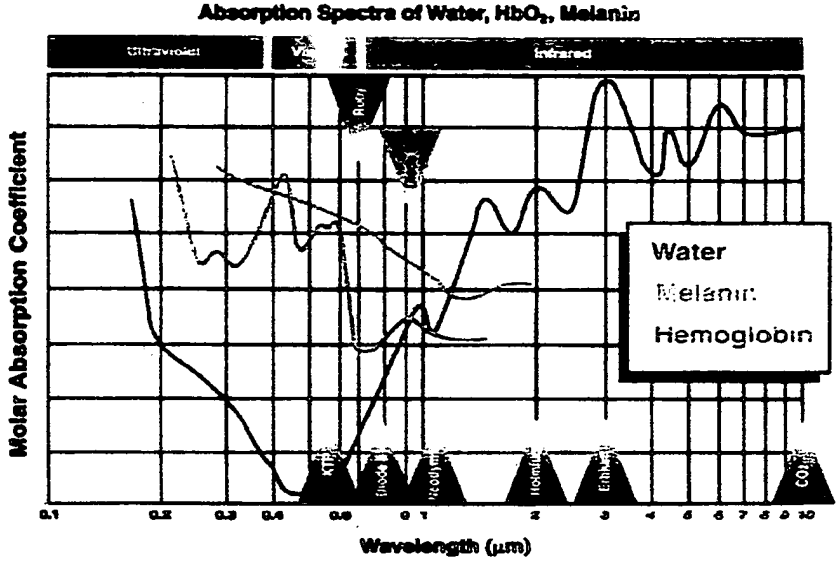
The Dornier **D940 Laser** Wavelength



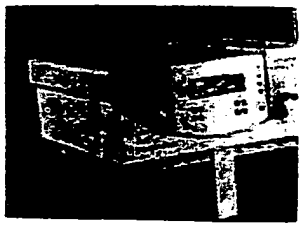
The highly unique light of a 940 nm wavelength ensures precise targeting of underlying tissue as it...

- Deep penetration
- Optimal absorption characteristics for hemoglobin (3x *more than an 810 or 1064 nm laser*)
- Optimal absorption characteristics for water (*10x more than an 810 nm laser, and 3x more than a 1064 nm laser*)
- Minimal melanin absorption when compared to other lasers (*3x less than an 810 nm laser, which enables treatment of darker skin-types*)

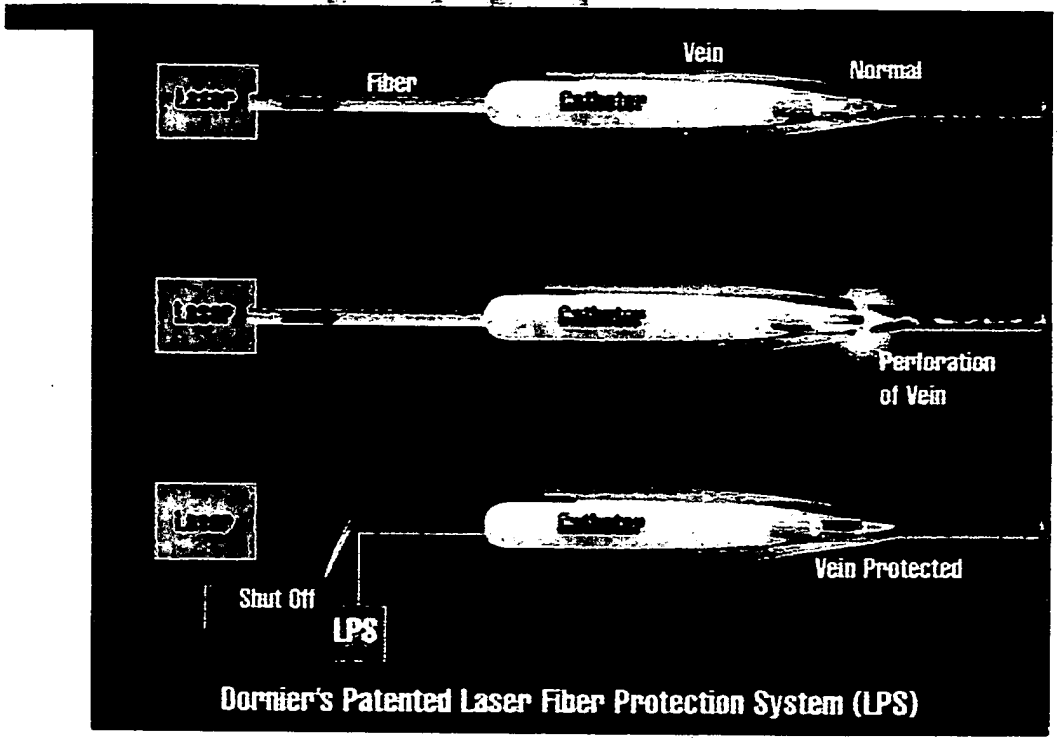
These absorption characteristics result in a safer and more effective treatment for vascular spider and varicose veins.

Built-in Safety While Performing Endovenous Treatments ...

The LPS Fiber Protection System



The Dornier D940



Dornier's Patented Laser Fiber Protection System (LPS)

Normal Operation
A normal fiber tip achieving optimal results on vein tissue layers.

No LPS Feedback
Fiber tip starts to char, absorbing laser light and producing unwanted damaging heat.

LPS Feedback
Tip has charred, triggering feedback and the LPS *shut off* for protection.

Technical Data

Wavelength
940 nm

Laser Power at Tissue
Pulse mode: 120 w
Continuous wave: 1-60 w

Aiming Beam
Red aiming beam standard
(Green beam option for better visibility)
Power 0-150mW adjustable

Laser Transmission System
Lightguides: core diameter 600µm
Lightguide connector: SMA modified

Application Modes
Pulse: removal of unwanted hair; vascular treatment
Standard: coagulation/ablation
Fiberlum, contact cutting
ELF: interstitial coagulation

Pulse Mode
Pulse energy: up to 10J
Pulse duration: 10-100 ms
Pulse interval: 200 ms-2 s
or Pulse repetition: up to 5 Hz

Record
Simultaneous display of *applied* energy, irradiation time and number of pulses

Power Supply
100-240 V, 50/60 Hz, 1.3 KVA

Dimensions (HxWxD) 8"x19"x20"

Weight
55 pounds

Standards/Classifications
IEC 601, IEC 825 European medical device directive Device protection class I, BF
Laser class IV

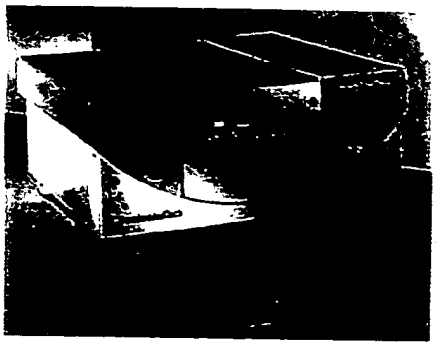
The Dornier D940 laser system is a must for any serious vein center or physician in practice.

About Dornier MedTech ...
Specializing in lithotripters, orthopedic shock wave devices, urotables and medical lasers, Dornier *MedTech* has operating units and service partners throughout the world - and continues to maintain its commitment to the medical device industry by providing innovative therapeutic, diagnostic and service solutions for numerous medical fields.

"The Dornier 940 nm laser is the most effective to date for the treatment of spider veins. This same laser will also replace stripping in 85% of patients who have saphenous vein insufficiency."

Jean Bush, MD, FACS
Midwest Vein Treatment Clinic

Dornier MedTech Americas



Dornier D940 Diode Laser System

Dornier specifically chose the 940 nm wavelength to design the D940 diode laser system for the treatment of superficial veins, as well as saphenous vein insufficiency.

The Dornier D940 is the first and only laser to emit light at 940 nm and is engineered with the newest PowerBar® technology to provide high peak powers from a small package.

Weighing only 55 pounds, the Dornier D940 is lightweight and easily transportable, with a retractable handle and built-in wheels. Plugs into any 110-volt outlet and is backed by Dornier's nation-wide service organization.

The highly unique light of a 940 nm wavelength ensures precise targeting of vessels because of its:

- Deep penetration
- Optimal absorption characteristics for hemoglobin (5x more than an 810 or 1064 nm laser)
- Optimal absorption characteristics for water (10x more than an 810 nm laser, and 3x more than a 1064 nm laser)
- Minimal melanin absorption when compared to other lasers (3x less than an 810 nm laser, which enables treatment of darker skin-types)

These absorption characteristics result in a safer and more effective treatment for both spider and varicose veins

Close Window

Dornier *MedTech*

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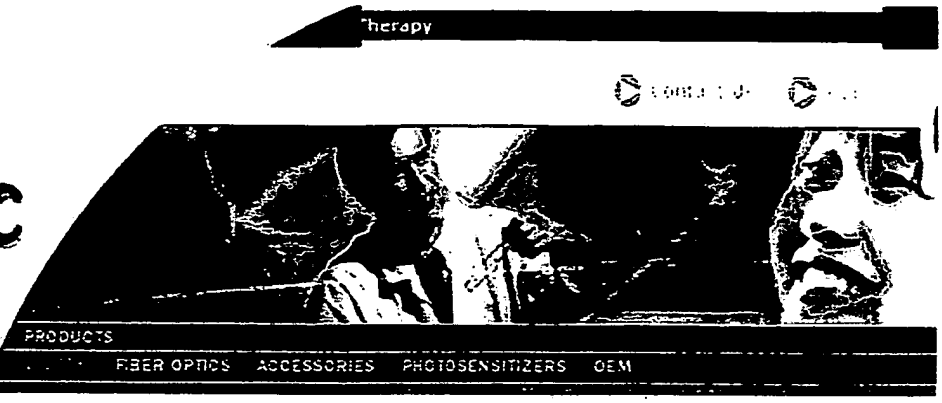

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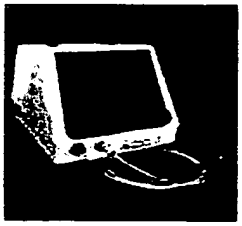
980nm Diode Laser Series



biolitec's 980nm Diode Laser Series, including the Ceralas D and SmilePro 980 Lasers, are ideal for soft-tissue applications in medical, dental, and veterinary environments.

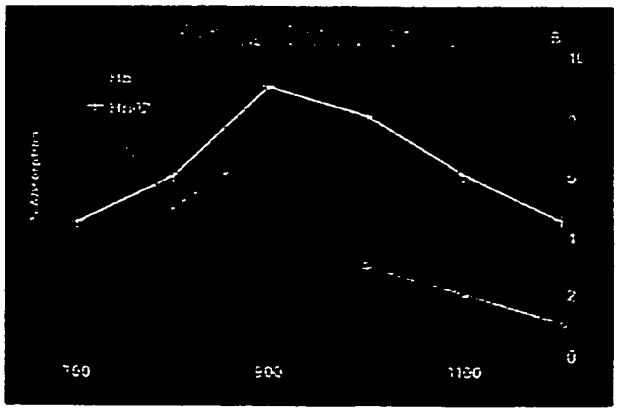
With unsurpassed, optimal absorption in water and hemoglobin, the 980 nm laser series allow controlled tissue ablation and provide a bloodless field for most surgical procedures. Unlike other medical lasers, **biolitec**'s 980nm lasers cut and coagulate optically — with negligible collateral tissue damage, charring, and recession. Many procedures using the 980nm lasers are pain-free, minimizing or even eliminating the need for anesthesia. These state-of-the-art 980nm lasers are compact and portable at 15 pounds and require no special cooling or maintenance.

More information about the SmilePro 980 for Dentistry.

More information about the Ceralas D for medical applications.

ELVeS™ – Endo Laser Vein System

ELVeS is a revolutionary new minimally-invasive laser treatment for superficial reflux of the greater saphenous vein - which may lead to varicose veins. Progressing the capabilities of vein treatments, ELVeS takes about 45 minutes and only local anesthesia is used - allowing patients to walk home after treatment! With virtually instant relief from venous reflux, patients can return to their normal lifestyle and activities immediately following treatment.



Other Laser Wavelengths

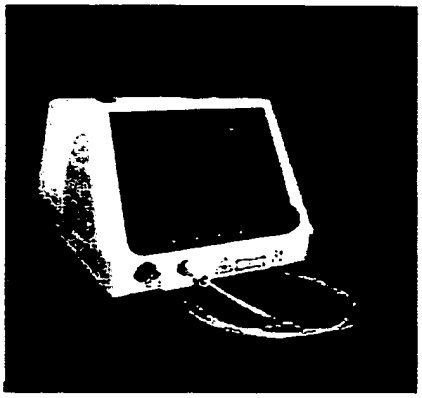
Other lasers' wavelengths are either absorbed too much or too little in water and / or hemoglobin and are consequently limited in several ways.

The 810 nm lasers' energy is eight times *less* absorbed in water than the 980 nm wavelength. Therefore, 810 nm lasers' fibers require 'conditioning' because their wavelengths can not properly ablate tissue. The conditioned tip of these lasers' fibers needs to heat up in order to work. In addition, the light energy from these lasers is absorbed in their fibers' tips – not in water, hemoglobin, or tissue. The laser light never reaches the patient - only the heat via a 'hot tip.'

Conductive heat is the only means of cutting and coagulating with lasers that require conditioned tips - which can damage collateral tissue and cause swelling, excessive necrosis, and patient discomfort.

The 980 nm Wavelength

A major benefit of the Ceralas D 980 nm Laser's unique wavelength is the ability to operate optically – *not via a 'hot tip.'* Because hemoglobin and water absorb the 980 nm wavelength at an optimal rate, the fiber tips of the Ceralas D laser do not require conditioning.



Because the Ceralas D exhibits superior control and minimizes collateral tissue damage, it is one of the most valuable and versatile lasers available today. "Although the 810 nm diode laser has been used for endovenous treatment, I feel it is not the best wavelength, as it does not absorb well in water," says John Mauriello, MD, a phlebologist in private group practice with offices in Charlotte and Durham, North Carolina. "The 940 nm diode laser is better than the 810 nm because it is on the up-slope of the water absorption curve. **But my research convinces me that 980 nm is the perfect wavelength because it is right on the peak of the water absorption curve."**

ELVeS FAQs

The ELVeS Procedure

Advantages of **biolitec**'s Endo Laser Vein System for Doctors

More Information for Patients

Attend a *King-Size* ELVeS Seminar!

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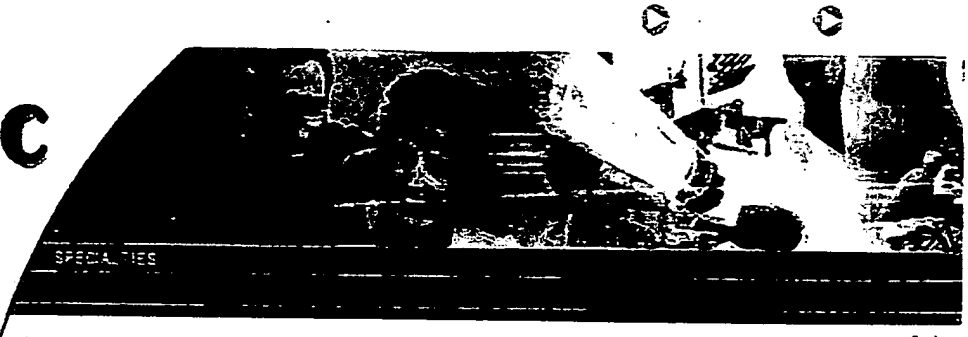

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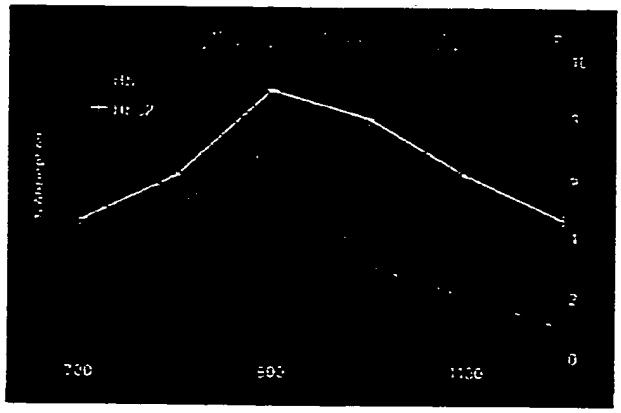
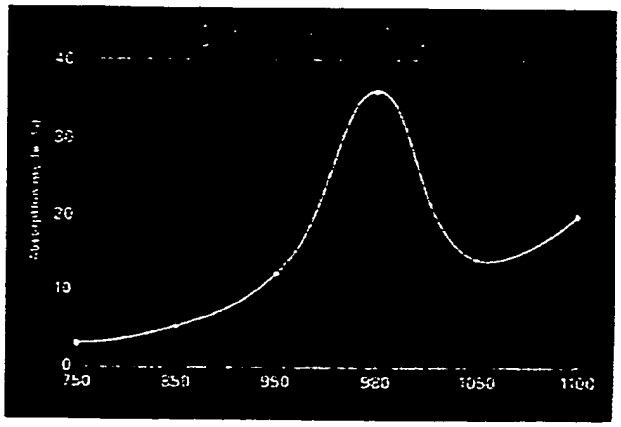
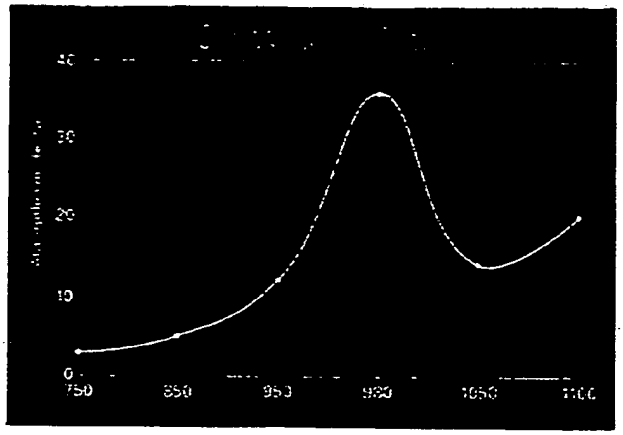
The Importance of a Laser's Wavelength: Advantages of 980 nm

A laser's wavelength determines many of its properties and capabilities. As a result of **biolitec's** extensive research in photobiology and laser physics, we have developed a series of 980 nm lasers that exhibit unparalleled lasing effects.

Since soft tissue contains a high percentage of water and hemoglobin, a laser's light energy must be well absorbed in both to cut and coagulate optimally. Considering the absorption characteristics of water and hemoglobin together, 980 nm is the ideal wavelength for soft tissue applications - including the ELVes Treatment for superficial reflux of the GSV, which often leads to varicose veins.







SmilePro 980 Technical Specifications

Laser Type	Integrated GaAlAs semiconductor laser arrays
Wavelength	980 nm
Output power	15 Watts
Power Range	1 - 15 W
Output power increments	1 Watt
Operating modes	Continuous or Pulsed
Pulse duration in On or Off modes	0.01 to 99.9 seconds
Aiming beam	Visible semiconductor (635 nm, red) < mW
Cooling	Air cooled
Weight	15 lbs
Dimensions	7" x 9" x 14" (h x w x d)
Power requirement	110 / 220 V

Ceralas D Technical Specifications

Laser Type	Integrated GaAlAs semiconductor laser arrays
Wavelength	980nm
Output power	15 W, 25 W, 50 W
Power Range	1 - 15 W, 1 - 25 W, 1 - 50 W
Output power increments	1 Watt
Operating modes	Continuous or Pulsed
Pulse duration in On or Off modes	0.01 to 99.9 seconds
Aiming beam	Visible semiconductor (635 nm, red) < mW
Cooling	Air cooled
Weight	14 lbs (15 W, 25 W); 19 lbs (50 W)
Dimensions	7" x 9" x 14" (15 W, 25 W); 7" x 15" x 16" (50 W)
Power requirement	110 / 220 V

For more information, contact your local sales representative or send an email to us at info@biolitec.com.

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Thermal Damage of the Inner Vein Wall During Endovenous Laser Treatment: Key Role of Energy Absorption by Intravascular Blood

T. M. PROEBSTLE, MD, MSc,* M. SANDHOFER, MD,† A. KARGL, MD,* D. GÜL, MD,* W. ROTHER, PHD,‡ J. KNOP, MD, PHD,* AND H. A. LEHR, MD, PHD§

*Department of Dermatology and §Institute of Pathology, University of Mainz, Germany, †Clinic for Dermatologic Surgery, Linz, Austria, and ‡Dornier MedTech Laser GmbH, Wessling, Germany

BACKGROUND. Despite the clinical efficacy of endovenous laser treatment (EVLT), its mode of action is incompletely understood.

OBJECTIVE. To evaluate the role of intravascular blood for the effective transfer of thermal damage to the vein wall through absorption of laser energy.

METHODS. Laser energy (15 J/pulse, 940 nm) was endovenously administered to explanted greater saphenous vein (GSV) segments filled with blood ($n = 5$) or normal saline ($n = 5$) in addition to GSVs under in vivo conditions immediately prior to stripping. Histopathology was performed on serial sections to examine specific patterns of damage. Furthermore, in vitro generation of steam bubbles by different diode lasers (810, 940, and 980 nm) was examined in saline, plasma, and hemolytic blood.

RESULTS. In saline-filled veins, EVLT-induced vessel wall injury was confined to the site of direct laser impact. In contrast, blood-filled veins exhibited thermal damage in more remote areas including the vein wall opposite to the laser impact. Steam bubbles were generated in hemolytic blood by all three lasers, while no bubbles could be produced in normal saline or plasma.

CONCLUSION. Intravascular blood plays a key role for homogeneously distributed thermal damage of the inner vein wall during EVLT.

W. ROTHER, PHD WAS AN EMPLOYEE OF DORNIER MEDTECH LASER GMBH. THE STUDY WAS SUPPORTED BY DORNIER MEDTECH LASER, WESSLING, GERMANY, AND BIOLITEC, JENA, GERMANY. T. M. PROEBSTLE, MD, MSC, M. SANDHOFER, MD, A. KARGL, MD, D. GÜL, MD, J. KNOP, MD, PHD, AND H. A. LEHR, MD, PHD HAVE INDICATED NO SIGNIFICANT INTEREST WITH COMMERCIAL SUPPORTERS.

RECENTLY, MINIMALLY invasive techniques have been clinically introduced for the effective treatment of varicose veins. In particular, VNUS closure[1,2] and endovenous laser treatment (EVLT)[3–5] have been shown to abolish reflux in the incompetent greater saphenous vein (GSV). Short-term efficacy has been reported as greater than 90%[1,2] and 95%,[3–5] respectively, comparing well with the results of classic surgery including high ligation and stripping of the GSV.[2] However, while the mode of action of VNUS closure has been studied in detail, the mechanisms of EVLT action are still not completely understood. It has been shown that EVLT, unlike VNUS, does not lead to occlusion of the vein by significant shrinkage of the vessel wall,[6] but instead causes a thrombotic occlusion of the laser-treated vein.[5]

Histopathologic examination of laser-treated veins revealed perforation of the vein wall at the site of direct laser impact and thermal damage of adjacent vein wall areas.[5,6] For the latter effect, laser-induced steam bubble formation has been postulated as the responsible mechanism,[5] implicating a putative role for intravascular blood serving as a chromophore absorbing the laser energy. In order, to further clarify the role of intravascular blood during EVLT, we performed comparative in vitro and in vivo experiments in the presence or absence of intravascular blood.

Patients and Methods

Administration of Laser Energy to GSV Samples

EVLT was applied as previously described in detail.[5] In brief, a 600 μm bare fiber with an outer diameter of 1.00 mm was connected to a 940 nm diode laser. Under in vivo conditions (see Patients), the fiber was inserted below the knee into the surgically exposed GSV. The fiber was advanced proximally to the point of high ligation of the GSV and subsequently withdrawn in steps of about 3–5 mm while

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laser energy was applied.[5] Identical laser parameters were chosen for the in vitro experiments with GSVs (see below).

In Vitro Experiments With GSVs

After classic varicose vein surgery of the GSV under tumescent local anesthesia,[7,8] the stripped vein segment was transferred to a saline bath at room temperature. The veins were cut into pieces 10 cm in length, and each piece was ligated at the proximal end before the laser fiber was inserted from the distal end. The vein was then filled either with heparinized blood (500 IU heparin/20 ml of blood) or with normal saline. After the distal end was ligated tightly around the laser fiber, single laser pulses of 15 J (15 W, 1 second) were delivered every 3–5 mm during stepwise withdrawal of the fiber tip. During the entire procedure the vein was bathed completely in normal saline solution. A total of 10 specimens, 5 filled with blood and 5 filled with normal saline during treatment, were subsequently fixed in formaldehyde, embedded in 1 mm rings in paraffin blocks, and studied histologically in routine hematoxylin and eosin stains on serial 5 µm sections. Each section was evaluated with respect to signs of thermal damage at the site of direct laser impact, at the adjacent area, and at more distant sites. Particular attention was given to the vein wall opposing the site of direct laser impact.

Patients

Two patients scheduled for classic varicose vein surgery under tumescent local anesthesia[7] consented to undergo experimental EVLT in the interval between high ligation and stripping of the GSV. One patient received EVLT with a blood-filled GSV. In the second patient, conditions were identical, apart from the fact that blood was washed out of the GSV and replaced by normal saline prior to EVLT. Complete replacement of blood by saline solution was confirmed visually by a flexible vascular fiberscope. The time interval between EVLT and invaginated stripping was 15 minutes. The vein was then cut into 2 cm sections, fixed in formaldehyde, and embedded in paraffin blocks for later histologic examination.

Laser-Generated Steam Bubbles in Normal Saline, Plasma, or Hemolytic Blood

An in vitro setup to measure laser-generated steam bubble sizes was used as previously described.[5] Diode lasers with 810 nm, 940 nm, and 980 nm were used with appropriate 600 µm fibers as provided by the manufacturers. Before starting the comparative experiments, the energy output of each device was calibrated at the fiber tip with a power meter. Before each experiment, the fiber tips were freshly cut to avoid secondary carbonization effects. Each laser wavelength was tested in tubes filled with normal saline, human plasma, and hemolytic blood by administration of pulses between 3 and 16 J. Plasma was obtained by centrifugation of heparinized blood for 20 minutes at 2000 g. Hemolytic blood was produced by replacing the removed plasma with equal volumes of distilled water.

Results

EVLT was performed under in vitro conditions on GSV segments either filled with blood ($n = 5$) or filled with normal saline ($n = 5$). In addition, EVLT was performed in vivo after high ligation but before stripping of the GSV, in a vessel filled with either blood or normal saline. The generation of steam bubbles in normal saline, plasma, and hemolytic blood was examined for laser wavelengths of 810, 940, and 980 nm under in vitro conditions.

Pathologic Examination of GSV Segments Receiving In Vitro EVLT

A minimum of 20 hematoxylin and eosin-stained serial sections of each vein segment were examined microscopically. Detectable changes of the vein wall, attributable to endovenous laser action, were highly reproducible. Figure 1 displays representative cross sections of laser-treated GSV segments. In saline-filled veins, vein wall damage was exclusively confined to the site of direct laser impact (Figure 1B), while adjacent regions (Figure 1A) and, in particular, the opposite side of the vein wall (Figure 1C) show virtually no signs of tissue damage. In contrast, pronounced thermal damage was detectable along the entire vein wall in blood-filled veins (Figure 1D,E), even at the vein wall opposite the laser impact (Figure 1F).

Pathologic Examination of EVLT Effects on Surgically Removed Veins

The histopathologic examination of veins stripped after EVLT under in vivo conditions showed a similar pattern of thermal damage as the veins treated under in vitro conditions described above. Figure 2 displays representative sections of laser-generated complete perforations of the vein wall produced from the saline-filled (Figure 2A,B) or blood-filled (Figure 2D,E) vein. Again, the immediate site of laser impact exhibited a comparable extent of coagulative necrosis, regardless of whether the vein contained saline (Figure 2A) or blood (Figure 2D). However, even the immediately adjacent inner vein wall showed distinct differences in the extent of thermal damage (Figure 2A,B,D,E), with severe injury in the blood-filled vein and a virtually normal situation in the saline-filled vein. Also, the vein wall located at the opposite site of the laser impact showed heat damage in the blood-filled vein (Figure

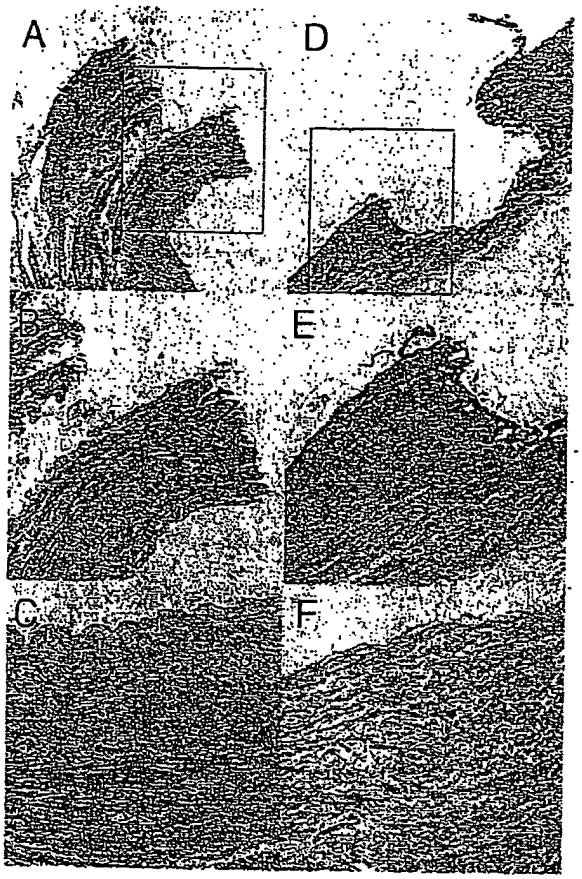

Figure 1. Representative hematoxylin and eosin sections of GSV segments after in vitro EVLT of A–C) saline filled veins or D–F) veins filled with heparinized blood. Under both conditions, direct laser impact causes perforation (A,B) or pronounced tissue ablation with focal coagulation necrosis at the immediate site of impact (D,E). In contrast to the saline-filled vein (A,B), the blood-filled vein exhibits more intensive and more remote injury to the adjacent vein wall areas (D,E). Likewise, superficial coagulative injury to endothelium, intima, and inner media are seen in vein wall areas on the opposite side of the laser impact in blood-filled veins (F), but are virtually absent in saline-filled veins (C). At most, slight tissue edema may be seen (C). Original magnification 55× (A,D) and 140× (B,C,E,F).

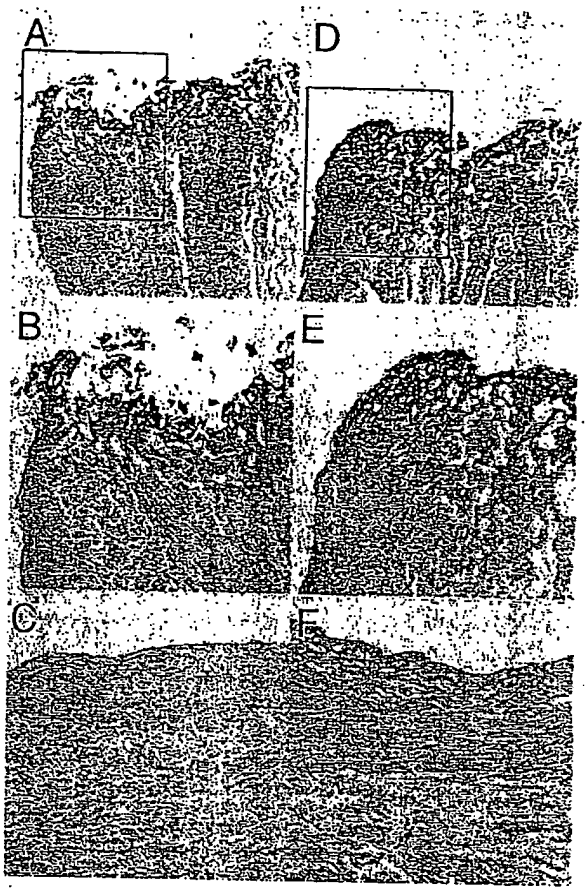

Figure 2. Histopathologic results of in vivo EVLT obtained from A–C) saline-filled or D–F) blood-filled veins. Arrangement of the panels as well as histomorphologic changes are identical to those described in Figure 1 and in the Results section of the manuscript.

2F), while in the saline-filled vein, only minimal laser-induced thermal damage was observed (Figure 2C).

Laser-Induced Steam Bubbles in Normal Saline, Plasma, and Hemolytic Blood

For laser wavelengths of 810, 940, and 980 nm, steam bubble volumes were plotted against the administered pulse energy (Figure 3). If the tube was filled with normal saline or plasma, no wavelength was able to produce detectable steam bubbles with pulse energies up to 16 J (data not shown). In contrast, in tubes filled with hemolytic blood, steam bubble sizes showed an almost linear proportionality with the administered laser energy. Note that no major difference could be detected between the three laser wavelengths. This indicates that the absorption of all three lasers by hemolytic blood is strong enough to transfer the energy completely into heat.

However, we found that this was true only if fresh-cut fiber tips were used for each experiment. Otherwise carbonization of the fiber tip led to extremely high tip temperatures, causing additional generation of energy through combustion of organic compounds of the hemolytic blood (data not shown).

Discussion

Despite growing acceptance and a rapid clinical introduction of EVLT, the underlying mechanism of action of this novel technique is still not fully understood. In a recent report of Weiss[6] it was demonstrated in elegant animal studies that endovenous radiofrequency

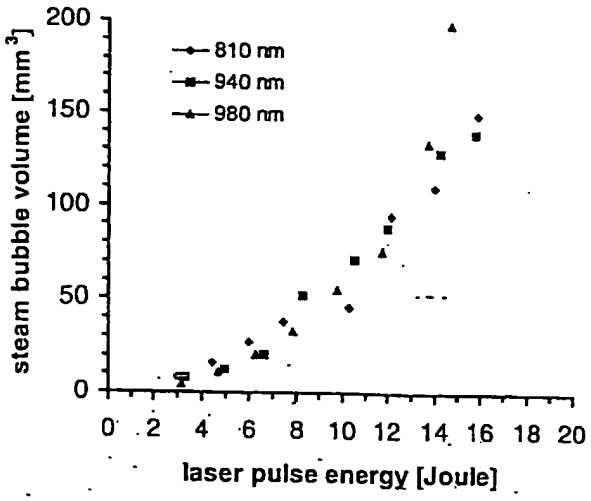

Figure 3. Laser-induced steam bubble volume in hemolytic blood plotted against delivered pulse energy for wavelengths of 810 nm (rhomboid), 940 nm (square), and 980 nm (triangle). No steam bubbles were produced with any of the experimental conditions in normal saline or plasma (data not displayed).

occlusion and EVLT have completely different modes of action. EVLT almost completely lacks the shrinkage effect of the vessels caused by prolonged exposure to moderate heat (85°C) in radiofrequency occlusion. Instead, EVLT causes perforation of the vein wall at the site of direct laser impact,[5,6] as a morphologic correlate for the consecutively observed perivenular ecchymoses.

In a previous report,[5] we proposed that laser-generated steam bubbles transfer a substantial amount of thermal damage to the vein wall during EVLT. These steam bubbles are created because of the high absorption of 940 nm laser energy in blood, with a technical penetration of only 0.3 mm. In water, this penetration depth is as much as 45 mm,[9] which is more than 100-fold deeper than in blood. Conversely, this implies that the absorption of 940 nm laser energy in water is less than 1% when compared to blood. Since under the particular topographic conditions of an endovascular laser fiber, a laser beam hits the vein wall within a markedly shorter distance than 45 mm, it can be concluded that heat generation by laser absorption cannot play a major role within a saline-filled vein. In this case, a laser beam of less than 1 mm diameter, with a fluence of more than 1500 J/cm², directly hits the vein wall, leading to complete perforating ablation of tissue (Figures 1A,B and 2A,B).

Our experimental setup tested this hypothesis under in vitro and in vivo conditions, providing histopathologic evidence: In a saline-filled vein almost the entire amount of focused laser energy is transferred to a small area at the vein wall, while in a blood-filled vein the thermal damage extends over a much wider topographic range of the inner vein wall, including the perilesional area and even areas opposite the immediate laser impact. This concordance between the in vitro and in vivo results suggests a sufficient correlation and validity of our in vitro model for the in vivo situation, despite the fact that under in vivo conditions the vein is much more compressed from outside by the presence of tumescent local anesthesia. However, one could speculate if a reduced, but still blood-filled, lumen of the vein could even facilitate laser-induced damage: relatively lower energies would suffice, because steam bubbles do not need to be generated in sizes that would be necessary to transfer homogenous damage to larger veins.

Evidence that blood plays not only a key role in absorption of 940 nm laser energy but also in absorption of 810 nm and 980 nm laser energy was provided by in vitro examination of steam bubble generation. While neither normal saline nor plasma were able to absorb laser energy substantially enough to generate steam bubbles, all three tested lasers produced comparable steam bubbles when exposed to hemolytic blood. Such steam bubbles, in all three laser systems, indicate that blood temperature passes the point of boiling at the site of the laser tip, thus transferring heat energy homogeneously to the inner vessel wall. The formation of these steam bubbles during EVLT could easily be monitored real time by duplex scanning, even allowing a continuous pullback of the laser fiber with the laser in continuous wave mode. One may speculate if with such a continuous pullback technique, perforations of the vein wall during EVLT could be avoided. However, a too-slow pullback velocity would certainly lead to a completely perforating longitudinal cut in the vein wall. Further experiments are needed on this topic. Therefore we hope that this improved knowledge about the exact mode of action of laser-induced vein damage may contribute to an improvement of endovenous laser treatment.

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Endovenous treatment of the greater saphenous vein with a 940-nm diode laser: Thrombotic occlusion after endoluminal thermal damage by laser-generated steam bubbles

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Purpose: Despite a rapid spread of the technique, very little is known about the laser-tissue interaction in endovenous laser treatment (EVLT). We evaluated EVLT of the incompetent greater saphenous vein (GSV) for efficacy, treatment-related adverse effects, and putative mechanisms of action.

Methods: Twenty-six patients with 31 limbs of clinical stages C_{2-6}, E_P, $A_{S,P}$, P_R with incompetent GSV proven by means of duplex scanning were selected for EVLT in an outpatient setting. A 600-μm fiber was entered into the GSV via an 18-gauge needle below the knee and proceeded to the saphenofemoral junction (SFJ). After infiltration of tumescent local anesthesia, multiple laser pulses of 15 J energy and a wavelength of 940 nm were administered along the vein in a standardized fashion. D-dimers were determined in peripheral blood samples 30 minutes after completion of EVLT in 16 patients and on postoperative day 1 in 20 patients. One GSV that was surgically removed after EVLT was examined by means of histopathology. Additionally, an experimental in vitro set-up was constructed as a means of investigating the mechanism of laser action within a blood-filled tube.

Results: A median of 80 laser pulses (range, 22-116 laser pulses) were applied along the treated veins. On days 1, 7, and 28, all limbs except one (97%) showed a thrombotically occluded GSV. In one patient, the vessel showed incomplete occlusion. The distance of the proximal end of the thrombus to the SFJ was a median 1.1 cm (range, 0.2-5.9 cm) in the remaining patients. Adverse effects in all 26 patients were ecchymoses and palpable induration along the thrombotically occluded GSV that lasted for 2 to 3 weeks. In two limbs (6%), thrombophlebitis of a varicose tributary required oral treatment with diclofenac. D-dimers in peripheral blood were tested with normal results in 14 of 16 patients 30 minutes after completion of the procedure and elevated results in 7 of 20 patients at day 1 after EVLT. However, an increase of D-dimers from day 0 to day 1 was observed in 15 of the 16 patients undergoing tests 30 minutes after EVLT and on day 1. The 940-nm laser was demonstrated by means of in vitro experiments and the histopathological examination of one explanted GSV to act by means of indirect heat damage of the inner vein wall.

Conclusion: EVLT of the GSV with a 940-nm diode laser is effective in inducing thrombotic vessel occlusion and is associated with only minor adverse effects. Laser-induced indirect local heat injury of the inner vein wall by steam bubbles originating from boiling blood is proposed as the pathophysiological mechanism of action of EVLT. (J Vasc Surg 2002; 35:729-36.)

For many patients of clinical stages C_2 to C_6 with proven incompetence of the saphenofemoral junction (SFJ) and refluxes along the greater saphenous vein (GSV), the standard surgical treatment still is high ligation of the vessel and its tributaries at the level of the SFJ, with subsequent stripping of the incompetent part of the GSV. In the last decade, less-invasive techniques have been further developed, particularly the use of tumescent local anesthesia facilitated ambulatory phlebectomy[1,2] or high ligation and stripping of the GSV.[3-5] In the last few years, a radiofrequency heating technique has been developed as an endoluminal approach with a distal, microsurgical vein access producing excellent cosmetic results.[6] One distinct major difference compared with classic varicose vein surgery is that endoluminal radio-frequency solely occludes the GSV without affecting tributaries at the level of the SFJ. Such a strategy is particularly remarkable, because it is generally accepted that recurrent varicose veins after surgery often have their origin in residual tributaries of the SFJ or in a residual saphenous stump. A recent study that suggested that, at least with short-term follow-up, extended ligation at the SFJ did not add much when compared with endoluminal closure of the GSV alone[7] raised a very controversial discussion. More recently, a similar minimally invasive technique, endovenous laser treatment (EVLT) of the GSV has been introduced,[8] and, in contrast to transcutaneous laser treatment of reticular veins and venulectasias,[9,10] we are only starting to learn about the

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Competition of interest: Dr Rother, who constructed the experimental set-up for in-vitro testing, is an employee of Dornier MedizinLaser GmbH, Germering, Germany.

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Table I. Characteristics of 31 treated limbs of 26 patients who underwent endovenous laser treatment, according to the CEAP classification

	Number of limbs (%)
Clinical stage	
C2 Varicose veins > 4 mm	31 (100)
C3 Edema	25 (81)
C4 Skin changes	11 (35)
C5 Healed ulcer	0 (0)
C6 Active ulcer	4 (13)
Etiology	
Primary	31 (100)
Secondary	0 (0)
Anatomy	
Superficial veins	31 (100)
Perforator veins	17 (55)
Cockett II/III	14 (45)
Sherman	3 (10)
Deep veins	0 (0)
Pathology	
Reflux	31 (100)
Obstruction	0 (0)

efficacy, adverse effects, and mode of action of this novel approach.

This study was conducted to obtain more detailed clinical and histopathological data on the application of EVLT in patients with clinical stages C_{2-6}, E_P, $A_{S,P}$, P_R, including an incompetent GSV. An in vitro set-up was developed and used as a means of further clarifying the mode of action of EVLT on the inner vessel wall.

METHODS

Patients. Patients were selected from our phlebology clinic as they came in for evaluation of specific complaints. As part of their routine examination, all patients underwent functional testing, including duplex scanning (Sonosite 180 plus, 4med, Erlangen, Germany). When a clinical stage C_2 to C_6 with an incompetent SFJ and reflux in the GSV were revealed by means of the phlebological examination, and thus an indication for high ligation and stripping was presented, patients were asked to choose between classic varicose vein surgery or EVLT. Only three of 29 patients preferred classic varicose vein surgery, whereas 26 patients chose EVLT. However, patients made this decision after reading information and an additional personal discussion with the physician about EVLT, which, in contrast to surgery, so far has no long-term follow-up, and the possible need for additional treatment measures, including classic surgery, later. Apart from the incompetent GSV, other incompetent superficial veins and perforator veins were tolerated, but not treated simultaneously to EVLT. Patients with secondary varicosis with deep vein reflux or deep vein obstruction were not able to undergo EVLT (Table I). All patients gave written informed consent in accordance to the Helsinki declaration.

Administration of laser energy. The whole EVLT procedure was exclusively limited to the GSV, and no additional measures like mini-phlebectomy or sclerotherapy were used as a means of treating tributaries of the GSV simultaneously. Roughly, the protocol was adapted from the paper of Navarro et al.[8] After duplex scanning-guided puncture of the GSV below the knee with an 18-gauge venous catheter (Vasofix, Braun, Melsungen, Germany), a J-tip guidewire (0.035-in, Medex Medical, Rossendale, UK) was advanced by means of duplex scanning control toward the SFJ. A 5F angio catheter (Infiniti, 100 cm, 0.97 mm, vertebral, Cordis Europe, 9301 LJ Roden, Netherlands) was shortened at the tip with a scalpel by approximately 5 cm to allow passage of the bare fiber more easily. The catheter was then forwarded over the guidewire until its tip was located approximately 1 cm distal to the SFJ. The guidewire was then removed and replaced by a 600-μm bare fiber with an outer diameter of 1.00 mm (Type D-6100-BF, Dornier MedizinLaser GmbH, Germering, Germany) connected to a 940-nm diode laser (Medilas D, Dornier MedizinLaser GmbH). With duplex scanning control, the laser fiber tip was passed through the tip of the angio catheter, thus extruding approximately 6 to 8 mm, with a final distance toward the SFJ of 1 to 2 cm. The correct location of the fiber tip could also be verified visually: in the darkened operation theater, the red (645 nm, 1 mW) pilot beam was detectable transcutaneously. Tumescent local anesthesia was then infiltrated along the GSV from the SFJ down to the point of access, as described elsewhere,[3] and given 5 minutes to establish the anesthetic effect before the start of the laser treatment. Laser energy was delivered in a pulsed fashion with a 1-second on and a 2-second off period. During the on period, 15 J of laser energy were delivered with a power of 15 W. During the off period, the fiber tip was retracted 5 to 7 mm. This cycle was repeated until a distance of 1 cm to the puncture site of the GSV was reached. In this manner, the laser treatment of the entire GSV lasted 3 to 5 minutes. Subsequently, the catheter was removed, and the patient received a full thigh class II compression stocking, resembling an ankle pressure of 30 mm Hg, and was advised to walk immediately. Additionally, as a precaution without any further rationale, low-molecular-weight heparin was administered subcutaneously for 5 days for thrombosis prophylaxis (Fragmin P, Pharmacia & Upjohn, Erlangen, Germany).

Concomitant duplex ultrasound scanning examination. All patients underwent duplex ultrasound scanning examinations before EVLT, during EVLT, and after EVLT on days 1, 7, and 28. During the course of the examinations, patients underwent scanning for refluxes in superficial veins, in the deep vein system, and also in perforating veins. Patients with an incompetent or occluded deep vein system were excluded from EVLT. Concomitant incompetent perforator veins or pathological findings in the superficial vein system were recorded, but did not prevent patients from receiving EVLT if the GSV was open and incompetent from the SFJ down to below the knee.

During EVLT itself, duplex scanning was particularly helpful in identifying the GSV at the puncture site, when necessary after full length down-scanning of the GSV from

the groin or up from the ankle. Duplex scanning was further an important means of localizing the precise position of the laser tip close to the SFJ before administration of tumescent local anesthesia, because afterward, because of the massive subcutaneous fluids, recognition of anatomical structures was almost impossible.

With scheduled duplex ultrasound scanning control examinations on days 1, 7, and 28, a full-length scanning of the treated vein was included as a means of demonstrating homogeneous thrombotic occlusion. Occlusive thrombosis was supposed when the vein was completely filled by an incompressible hypoechogenic mass and when no fluxes were detected within the vessel lumen. Similarly, in the region of the SFJ, the proximal ending of the thrombus was determined by means of compression and detection of fluxes. The distance of the proximal thrombus ending toward the junction with the deep femoral vein was measured. At day 28, the hypoechogenicity of the thrombus had almost disappeared. However, the lack of fluxes and the remaining incompressible vessel still allowed sufficient conclusions. Additional scanning of the deep vein system excluded a thrombotic affection there.

Testing for D-dimers in peripheral blood. After detection of EVLT-induced thrombotic occlusion, rather than an immediate closure of the GSV, we scheduled D-dimer testing for every patient. With the exception of the first six patients, D-dimer values (Tinaquant D-dimer, Roche Diagnostics, Mannheim, Germany) were scheduled to be determined from blood samples obtained 30 minutes and 1 day after the EVLT procedure. According to the manufacturer's data sheet, D-dimer values below 0.50 mg/L were considered to be within normal limits. However, because of technical reasons, blood sampling failed in four patients 30 minutes after EVLT.

Histopathologic examination. One patient gave informed consent to undergo EVLT as part of his routine varicose vein surgery procedure, which included extended high ligation of the SFJ and subsequent stripping of the incompetent parts of the GSV. EVLT was administered immediately after completion of extended high ligation, but before stripping of the GSV. The treated vein was left in place for another 15 minutes and then removed by means of stripping. The removed vein was photodocumented (Fig 1, *A*) and histopathologically examined with hematoxylin and eosin staining.

Mechanism of laser action. As a means of evaluating the mechanism of action of the 940-nm laser beam within the vein, an experimental set-up was designed (Fig 3, *A*). A silicone tube with an inner diameter of 6 mm was connected to a transparent tube with an inner diameter of 2 mm. The tube system was then filled with heparinized blood. From the opposite side, the laser fiber was inserted into the middle of the silicone tube. Different amounts of laser energy were then applied by means of variation of either laser power or pulse duration. With each laser pulse, the extension of the volume within the system was assessed by documenting the change in the blood level within the 2-mm tube. A cylindrical volume calculates as $V = h \times \pi r^2$ (eg, if a laser pulse produces a movement of the blood level of $h = 54$ mm, the laser generated steam volume calculates as $V = 54\ \text{mm} \times \pi[1\ \text{mm}]^2 = 170\ \text{mm}^3$, corresponding to a steam bubble length of 6 mm in a tube with a diameter of 6 mm). The temperature of the steam bubble is supposed to be close to 100° C and, once generated, should stay on this level constantly throughout its increase of volume, as it is known in the physics of phase transitions.

RESULTS

Twenty-six patients, 21 with unilateral and 5 with bilateral incompetent GSV, received EVLT by means of a 940-nm diode laser with tumescent local anesthesia. Nineteen patients were women (73%), and seven patients were men (27%), with 22 and 9 limbs treated, respectively. The median age of the patients was 57 years (range, 27-83 years). Before treatment, the median diameter of the GSV was 6.0 mm (range, 4.0-9.9 mm) at the level of the SFJ. In our relatively small cohort with a spectrum of clinical stages (Table I), the GSV diameter did not correlate with the body mass index of the patient (data not shown), the median of which was 26.6 (range, 20.0-39.7). The median amount of infiltrated tumescent local anesthesia was 650 mL per limb (range, 250-1000 mL).

Technical skills. Initially, before the use of duplex scanning for guided puncture of the GSV, access to the GSV failed in two of seven patients. These two patients underwent subsequent classic surgery. In four additional cases, insertion of the guidewire from below the knee to the SFJ was not possible in one step because of pronounced tortuosity of the GSV. In three of these four cases, an additional puncture of the GSV approximately 15 cm above the knee allowed treatment in two parts. In one case, EVLT was limited to the proximal 20 cm of the GSV because of the technical inability to obtain access to the more distal part of the GSV.

However, in all cases, duplex scanning-controlled placement of the fiber tip was achieved within a distance of 1 to 2 cm distal from the SFJ. In patients who were not overtly obese, this position could be visualized by means of transcutaneous illumination of the pilot laser beam. In our series of 31 limbs in 26 patients, this was true in four limbs of three male patients with a body mass index between 31.5 and 39.7. However, even in those obese patients, transcutaneous detection of the laser pilot beam was possible after applying gentle pressure to the overlaying skin.

Effects of endovenous laser treatment. During step-wise removal of the laser fiber, a median of 80 pulses (range, 22-116) of 15 J energy each were delivered, corresponding to a distance of 5 to 7 mm between laser pulses.

On days 1, 7, and 28 after treatment, thrombotic occlusion of the GSV was noted in all cases. In 30 of 31 limbs (97%), the thrombotic occlusion was complete from the distal puncture site, reaching proximally up to a median distance of 1.1 cm (range, 0.2-5.9 cm) from the SFJ. In one limb, the proximal occlusion of the GSV failed over a length of 20 cm despite complete occlusion of more distal parts of the GSV. The diameter of the GSV at the SFJ was 9.9 mm

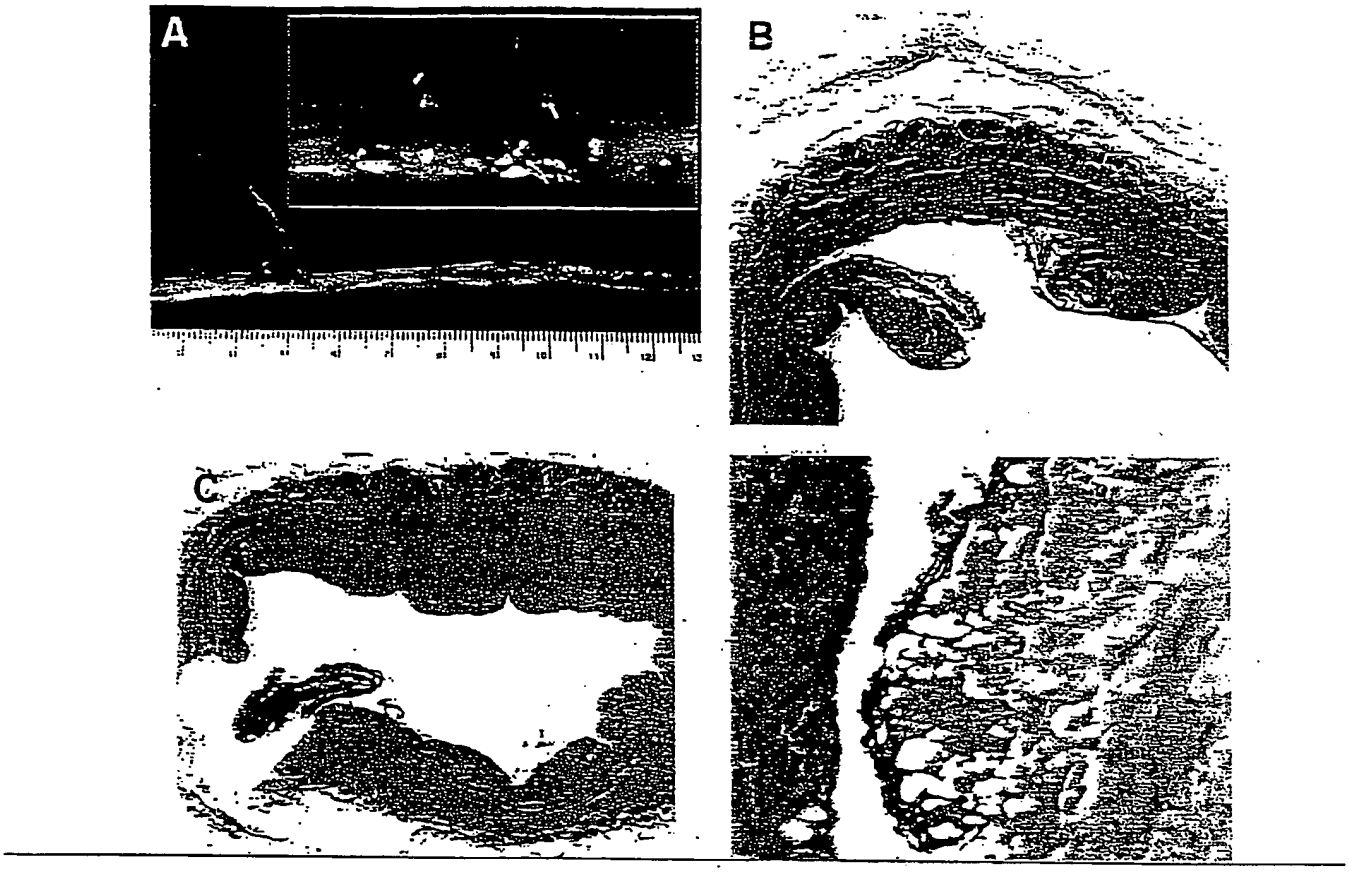


Fig 1. Macroscopic and microscopic hematoxylin and eosin-stained histopathologic examination of a GSV that has undergone EVLT before stripping. A, Outer surface of the endovenously laser-treated GSV. Dark spots resembling carbonization, or even full perforation of the vein wall, were caused by direct impact of the 940-nm laser beam. B, Intimal tear next to a non-perforating laser hit. C, Vein wall disruption caused by direct laser impact. D, High magnification of the margin area of vein wall disruption showing pronounced thermal damage, including carbonization.

and, therefore, the largest diameter of the whole series. Additionally, in this patient, we found by means of duplex scanning control a large caliber tributary with high blood flow feeding the GSV at the distal open point.

Adverse effects. After the local anesthetic effect subsided after EVLT, slight to moderate local pain was reported by all patients over the treated vein. Also, moderate ecchymoses, most likely caused by laser-induced perforation of the vein wall, could be observed in every patient at the inner thigh and knee region from the next day to approximately 2 weeks later. However, these ecchymoses were not as pronounced as they are usually with classic varicose vein surgery, and no hematoma was found. For the first 2 to 3 weeks after EVLT, also a slightly shorter period than frequently observed with classic surgical procedures, an induration was palpable along the treated GSV, and this was experienced by the patients as slight to moderate pain during extended movement of the leg. A thrombophlebitic reaction developed within an untreated varicose tributary at the distal thigh in two patients 2 and 5 days after EVLT. Oral treatment with diclofenac (75 mg, slow release, three times a day) resulted in immediate pain control. Hyperpigmentation developed in one patient over the thrombotically occluded GSV, which was still visible at 4 weeks after EVLT. All other patients were free of adverse effects at 4 weeks after the procedure. No other adverse effects or complications were reported.

D-dimers in peripheral blood. In 16 patients, D-dimer levels in peripheral blood were evaluated immediately after EVLT, and in 20 patients, blood samples were drawn on day 1 after EVLT (Table II). D-dimer levels were tested with normal results in all samples except one obtained 30 minutes after EVLT, with a median value of 0.39 mg/L (range, 0.09-0.80 mg/L). When D-dimer levels were tested at day 1 after EVLT in 20 patients, a median of 0.43 mg/L (range, 0.24-1.73 mg/L) was found. However, only seven blood samples showed D-dimer levels exceeding the upper limit of 0.50 mg/L. Although the

Table II. D-dimer levels in peripheral blood of patients who underwent endovenous laser treatment

	30 minutes after EVLT	*1 day after EVLT*	*Ratio 1 day/30 min*
Patients with1 limb treated	Median 0.30 mg/L (range 0.09-0.80) n = 13	Median 0.33 mg/L (range 0.24-1.73) n = 16	Median 1.39 (range 0.88-3.67) n = 13
Patients with 2 limbs treated	Median 0.45 mg/L (range 0.44-0.48) n = 3	Median 0.68 mg/L (range 0.50-0.91) n = 4	Median 1.82 (range 1.15-2.02) n = 3
All patients	Median 0.39 mg/L (range 0.09-0.80) n = 16	Median 0.43 mg/L (range 0.24-1.73) n = 20	Median 1.43 (range 0.88-3.67) n = 16

EVLT, Endovenous laser treatment.

absolute values remained mostly within normal limits, D-dimer levels were shown by means of intraindividual evaluation to increase from day 0 to day 1 in 15 of 16 patients who underwent both tests. The median increase ratio was 1.43 (range, 0.88-3.67), reflecting the process of thrombotic occlusion of the GSV. When separating the patients who received unilateral EVLT from patients who had a bilateral procedure (Table II), it looks as if patients with both limbs treated did not present the very low D-dimer values that are occasionally observed in patients with one limb treated. This observation might relate to two thrombotic processes instead of one, but also might be influenced by the thrombotic process having proceeded somewhat more in the first limb of those patients with bilateral EVLT. Unfortunately, the numbers are small in Table II and therefore do not warrant statistical analysis.

Pathologic examination of the endovenous laser treatment stripped vein. Macroscopically, the vein wall showed reddening, carbonization, or even perforation at those sites where the fiber tip was closest to the vein wall during delivery of laser energy (Fig 1, *A*). Either gross vein wall destruction associated with direct impact of the laser beam (Fig 1, *B-D*) or less pronounced heat-mediated vein wall injury (Fig 2, *B, C*) was demonstrated by means of microscopical examination of corresponding hematoxylin and eosin-stained slides. The heat injury demonstrated in Fig 2, *B* and *C*, was consistently detectable along the distance of 5 to 7 mm of vein wall, between the direct impact of two laser impulses, and is, in our opinion, the basis of a subsequent homogeneous thrombotic occlusion of the vessel. At those sites of direct laser action, the most destructive patterns of tissue damage can be observed: perforating and non-perforating vaporization of the vein wall, carbonization of the adjacent tissue margins, and intimal tear in response to the explosion-like delivery of high energy densities, called photo-disruption. However, because a stripping was performed after EVLT, some of the destruction observed, like intimal tears, may originate from the stripping procedure itself.

Mechanism of action of the 940-nm diode laser. Administration of different amounts of laser energy in the in vitro set-up was used as a means of evaluating the putative mechanism of laser action within the vein (Fig 3). During the experiments with heparinized blood in a silicone tube, we observed that a steam bubble formed during delivery of laser energy, and it collapsed immediately after discontinuation of the laser pulse. When we plotted the maximum volume of the laser-generated steam bubble against the amount of laser energy delivered, it showed a linear correlation (Fig 3, *C*). As calculated in the Methods section, a typical laser pulse with an energy of 15 J produced a steam-bubble of approximately 6 mm in a 6-mm diameter vessel. As shown in Fig 3, *C*, the formation of a steam bubble required a threshold energy of about 1.5 J. This threshold energy is needed to heat up the surrounding blood until it reaches boiling temperature. A laser pulse energy below this level would only heat the blood, without any steam bubble formation.

DISCUSSION

The principal finding in this study is that EVLT with a 940-nm diode laser system, when performed under tumescent local anesthesia, is a clinically feasible and well-tolerated technique. Because of vein access via an 18-gauge needle, it is a truly minimal invasive procedure, leaving a virtually invisible scar on the patient's skin.

The efficacy of EVLT in obtaining early occlusion of the GSV is very satisfactory. Even if these are very early results, immediate closure rates of 97% in our series and 100% reported by another group with the 810-nm diode laser[8] provide a rationale for further evaluating this new method.

A major emphasis of this study was placed on the mode of action of this novel technique: technically, the depth of penetration of a 940-nm laser beam into blood is only approximately 0.3 mm.[11] Also, the laser beam remains focused to a very small spot after leaving the fiber tip. Although these characteristics of the laser beam could explain a focal perforation of the vein wall (Fig 1, *C, D*) immediately adjacent to the fiber tip, this would not adequately explain the widespread injury to the vein wall observed in the vicinity of the perforation sites (Fig 2, *B, C*). With our in vitro set-up, we could identify steam bubble formation at the laser tip (Fig 3, *B*). The volume of the laser-generated steam bubble correlated directly to the laser energy (Fig 3, *C*). Because such a

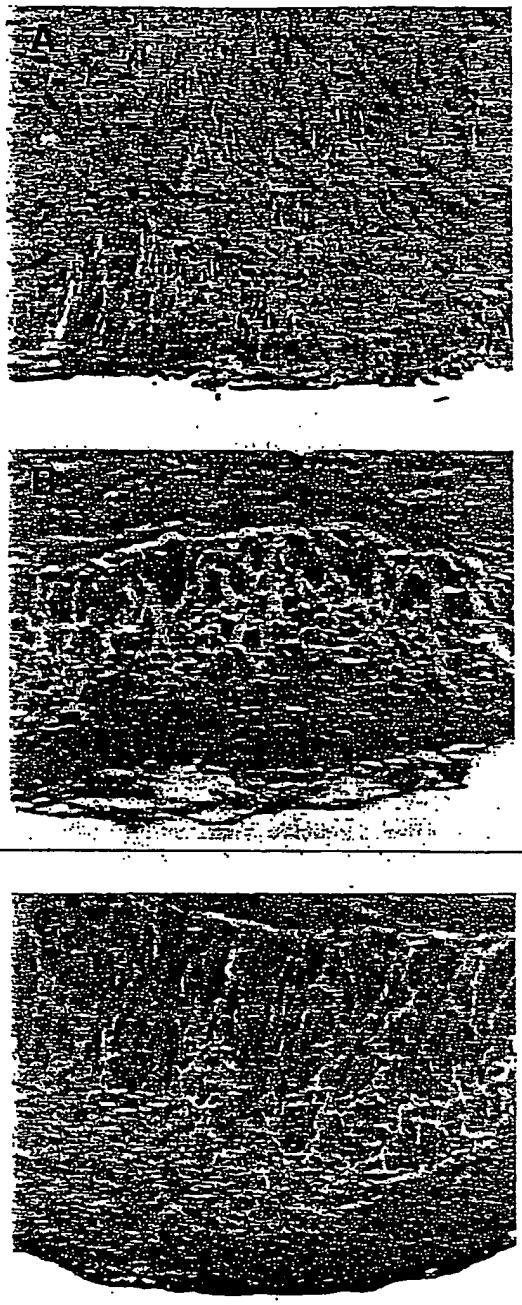


Fig 2. Indirect, steam bubble-mediated thermal damage after EVLT, several millimeters away from areas of direct laser impact. A, Control: normal varicose vein after stripping without earlier EVLT, with intact endothelium and distinct cellular contours. The nuclei are round to oval. B, EVLT resulted in a lift-off of endothelial cells, a denudation of the intima, loss of cellular contours, and fibrin deposition. Additionally, some areas show marked vacuolization of cells or even spongiosis. C, Swelling and waxy homogenization of collagen: Focal coagulation necrosis within the intima.

steam bubble formation is expected to occur within the vein lumen during EVLT, we propose that this phenomenon accounts for the thermal injury to an extended surface of the inner vein wall.

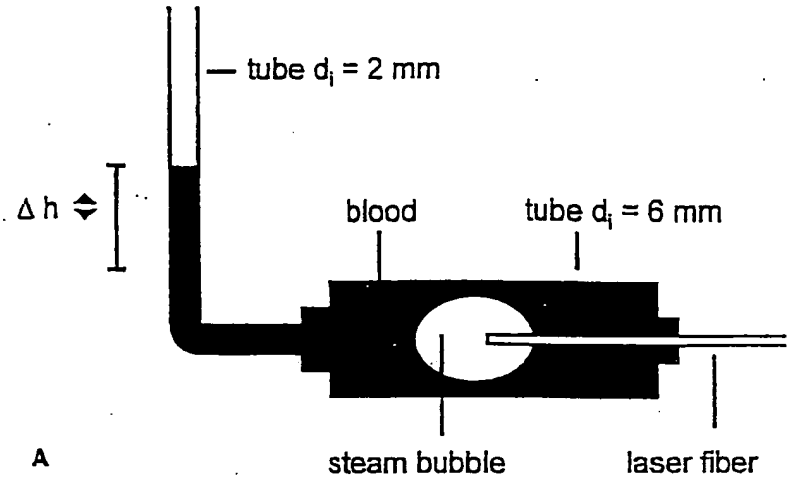
In a recent paper, Sadick et al[10] reported histopathological alterations of reticular veins and venulectasias after transcutaneous neodymium/yttrium-aluminum-garnet laser treatment that compare well with our findings. This opens the question of whether also in transcutaneous laser treatment of smaller veins the crucial damage of the vein may involve a similar steam bubble-mediated, hence indirect, thermal injury, rather than the immediate highly focused damage by the laser beam itself.

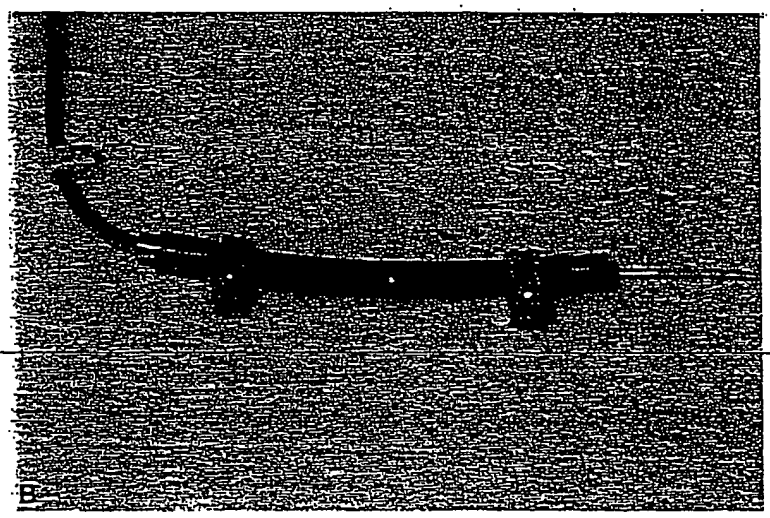
Steam bubble formation is a local, instantaneously reversible phenomenon that, after collapse of the bubble, poses no risk, such as gas embolism, to the patient. However, the extensive heat damage of the endothelium and the intima does induce the desired effect: full-length thrombotic occlusion of the vein. The complete thrombotic occlusion, however, is not detectable immediately after EVLT, but can be recognized at day 1 by means of a simple duplex scanning examination, which shows an incompressible, hypoechogenic cord in the lumen of the saphenous vein. This thrombotic occlusion is also reflected in all patients with an increase of D-dimer levels in peripheral blood by a median factor of 1.43. Because in our study and another study[5] no EVLT-induced deep vein thrombosis occurred, it seems very unlikely that the EVLT-induced thrombotic process of the GSV has a concomitant risk for deep vein thrombosis, as is known for superficial thrombophlebitis.[12] However, it remains unclear whether such an hypothetical risk of deep vein thrombosis does indeed exist or whether it is only so much lower compared with superficial thrombophlebitis[12] that it can only be detected in a larger series of patients.

Other commonly observed adverse effects with EVLT are induration along the GSV and mild-to-moderate ecchymoses. These ecchymoses, present for approximately 2 weeks, could be a cosmetic problem for patients who are expecting a minimally invasive, barely invisible treatment of their GSV incompetence. In this respect, EVLT would compare unfavorably with endoluminal radio-frequency closure. However, when weighed against the potential nerve damage after endoluminal radio-frequency treatment with subsequent skin paresthesis in as many as 16% of patients,[7] such an entirely reversible adverse effect seems quite acceptable.

Less frequent adverse effects, like thrombophlebitis of untreated tributaries or appearance of hyperpigmentation along the GSV, need to be followed and documented as the number of patients and EVLT procedures increase. At least the risk of thrombophlebitis could be avoided completely if varicose tributaries, unlike in the present series, are treated in the same session (eg, with mini-phlebectomy).[1,2]

Finally, it remains to be established whether EVLT induces effective long-term occlusion of the treated veins. Recurrent reflux, either originating from the SFJ or neoc-





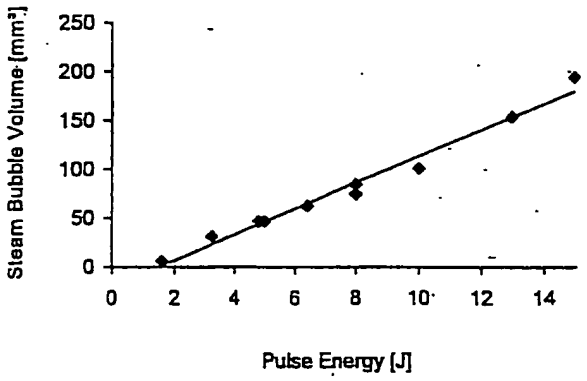


Fig 3. A, Schematic drawing of the in-vitro set-up for examining the laser-generated steam bubble formation. The laser fiber was inserted into a silicone tube of 6-mm-diameter filled with heparinized blood. During delivery of laser energy, heating and boiling of the blood finally lead to the formation of a steam bubble, pushing the corresponding blood volume out of the tube. Thus, the movement of the blood level in the smaller 2-mm-diameter tube allowed the calculation of the volume of the steam bubble in reverse. B, Visible steam bubble formation during delivery of a laser pulse of 15 J. C, Dependency of the steam bubble volume for various amounts of energy delivered by the laser beam.

curring within recanalized parts of the GSV, has to be followed closely. Only long-term follow-up in prospective trials will be able to answer this question.

We thank Mrs Weingärtner for skilled technical support and Mrs Gärtner for excellent preparation of the samples for histopathological examination.

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Submitted Aug 15, 2001; accepted Oct 12, 2001.

APPENDIX 3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/699,212	Confirmation No.: 2780
Applicant	:	David R. Hennings et al.	
Filing Date	:	October 30, 2003	
Title	:	Endovenous Closure of Varicose Veins with Mid Infrared Laser	
Group Art Unit	:	3739	
Examiner	:	David M. Shay	
Docket No.	:	15487.4002	
Customer No.	:	34313	

Mail Stop AMENDMENT
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DAVID R. HENNINGS

I, David R. Hennings, do declare and say as follows:

1. I am one of the inventors named in the above-identified application.

2. Attached hereto as Exhibits A-E are, respectively, true copies of product literature published by Dornier MedTech, biolitec, AngioDynamics, Vascular Solutions and Diomed, respectively.

Further, Declarant sayeth not:

CERTIFICATE OF MAILING (37 CFR §1.8)

I hereby certify, pursuant to 37 CFR §1.8, that I have reasonable basis to expect that that this paper or fee (along with any referred to as being attached or enclosed) would be mailed or transmitted on or before the date indicated with the United States Postal Service with sufficient postage as first class mail on the date shown below in an envelope addressed to Mail Stop Amendment, Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450.

Dated: July 5, 2005

Lynne Fulmer

Applicant	:	David R. Hennings et al.
Appl. No.	:	10/699,212
Examiner	:	David M. Shay
Docket No.	:	15487.4002 (Formerly NSL-501)

I declare under penalty of perjury that the foregoing is true and correct. Executed this 30 day of June, 2005 at Roseville, California.

David R. Hennings

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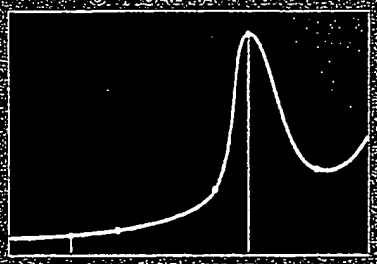

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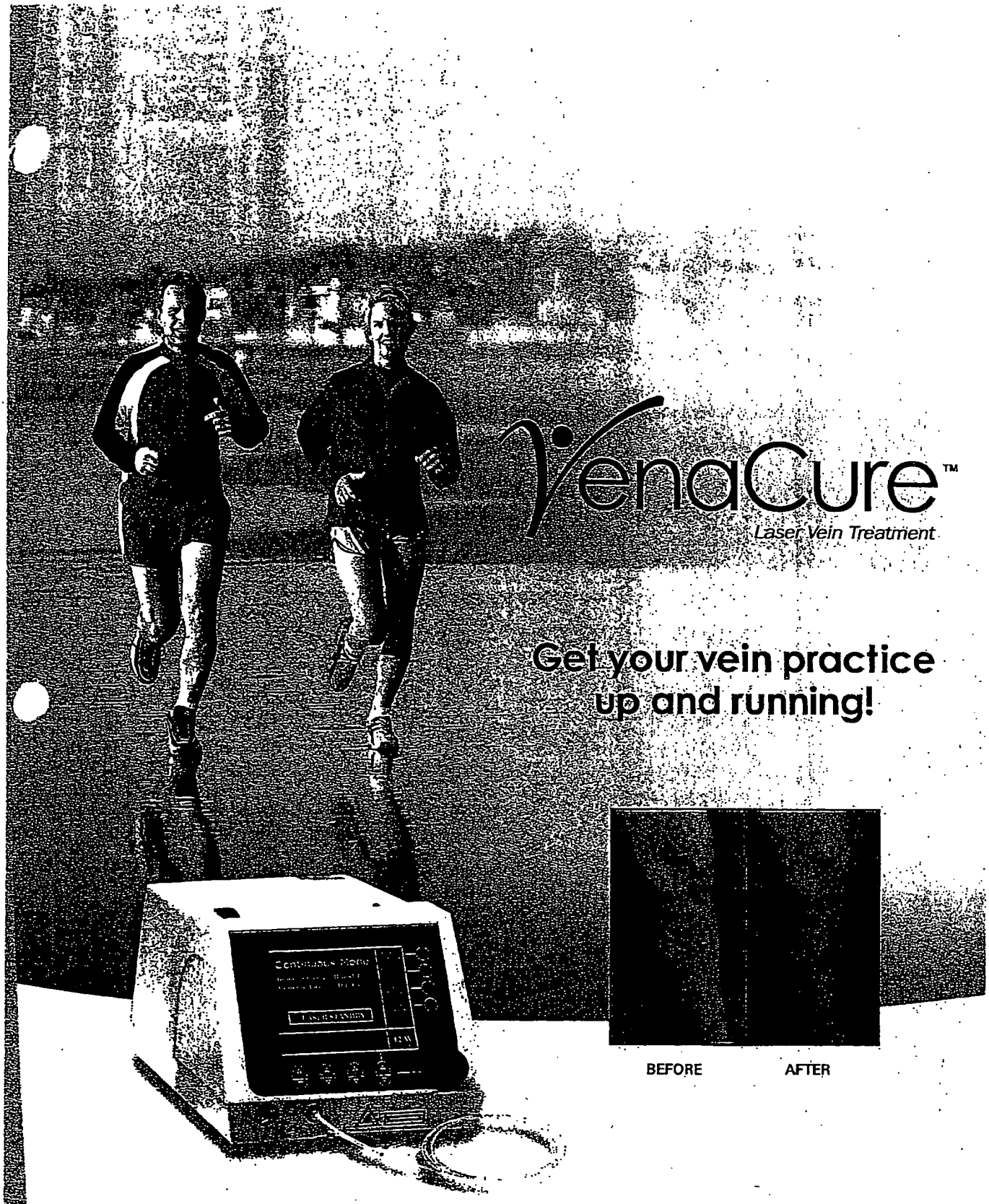

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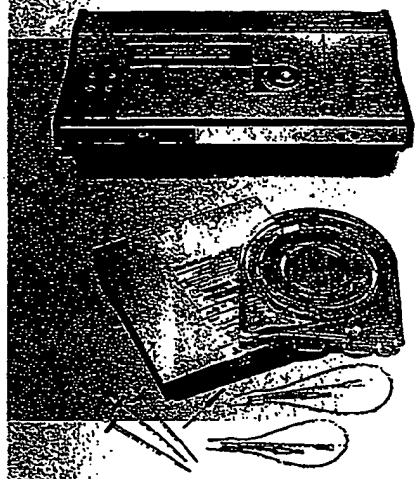

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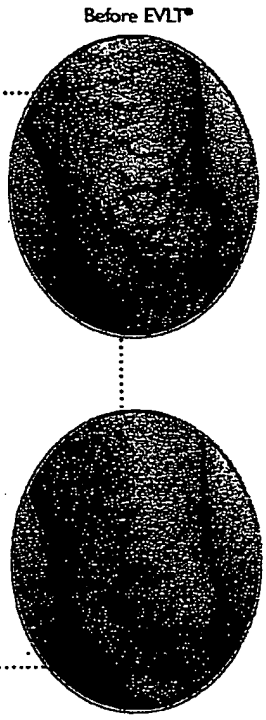

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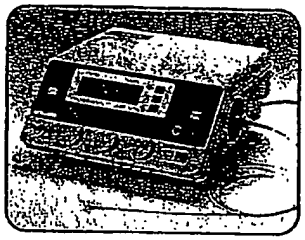
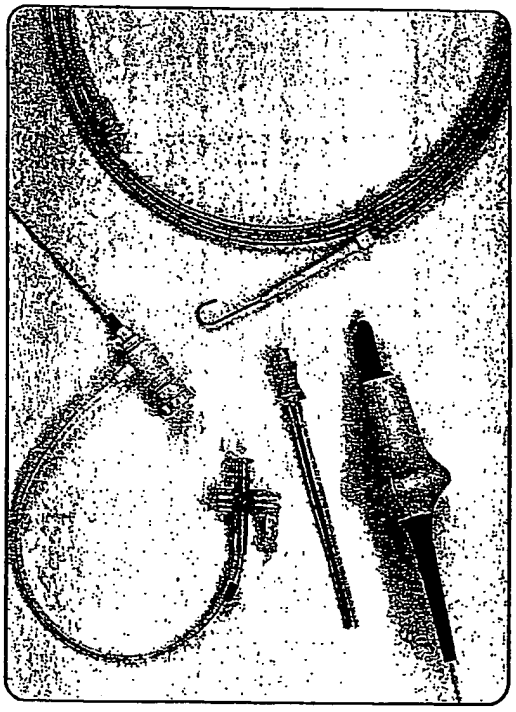
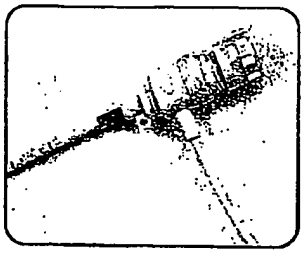


A red aiming beam identifies the exact position of the fiber within the vein.





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